National Institute on Drug Abuse

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# Medication Development for the Treatment of Cocaine Dependence: Issues in Clinical Efficacy Trials

175

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# Medication Development for the Treatment of Cocaine Dependence: Issues in Clinical Efficacy Trials

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# Contents

Preface . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 1
*Betty Tai, Charles V. Grudzinskas, Nora Chiang, and Peter Bridge*

Goals and Rationale for Pharmacotherapeutic Approach in Treating Cocaine Dependence: Insights From Basic and Clinical Research . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 5
*Mary Jeanne Kreek*

Overview of Potential Treatment Medications for Cocaine Dependence . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 36
*Elinore F. McCance*

Methodologic Recommendations for Cocaine Abuse Clinical Trials: A Clinician-Researcher's Perspective . . . . . . . . . . . . . . . . . . 73
*Edward V. Nunes*

Management of Clinical Trials With New Medications for Cocaine Dependence and Abuse . . . . . . . . . . . . . . . . . . . . . . . . . . . . 96
*Ari Kiev*

Outcome Measurement Considerations: Pharmacological Treatments for Substance Abuse . . . . . . . . . . . . . . . . . . . . . . . . . 118
*Karla Moras*

Variability in Treatment-Seeking Cocaine Abusers: Implications for Clinical Pharmacotherapy Trials . . . . . . . . . . . . . . . . . . . . . . . . 137
*Kathleen M. Carroll, Charla Nich, and Bruce J. Rounsaville*

Baseline Assessment, Study Entry, and Stabilization: Double-Blind Clinical Trials in Drug Dependence . . . . . . . . . . . . . . 158
*John Grabowski, Gila Arnoni, Ronith Elk, Howard Rhoades, and Joy Schmitz*

The Addiction Severity Index in Clinical Efficacy Trials of Medications for Cocaine Dependence . . . . . . . . . . . . . . . . . . . . . . . . . 182
*John S. Cacciola, Arthur I. Alterman, Charles P. O'Brien, and A. Thomas McLellan*

Cognitive-Neuromotor Assessment of Substance Abuse: Focus on Issues Related to Cocaine Abuse Treatment . . . . . . . . . . . 192
*E.H. Ellinwood, Jr. and T.H. Lee*

Treatment Effectiveness Score as an Outcome Measure in Clinical Trials . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 208
*Walter Ling, Steven Shoptaw, Donald Wesson, Richard A. Rawson, Margaret Compton, and C. James Klett*

Pharmacokinetics of Cocaine: Considerations When Assessing Cocaine Use by Urinalysis . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 221
*Reese T. Jones*

Quantitative Urine Levels of Cocaine and Other Substances of Abuse . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 235
*Jeffery N. Wilkins*

Use of Quantitative Urinalysis in Monitoring Cocaine Use . . . . . . . 253
*Kenzie L. Preston, Kenneth Silverman, Charles R. Schuster, and Edward J. Cone*

Is Quantitative Urinalysis More Sensitive? . . . . . . . . . . . . . . . . . . . . 265
*Shou-Hua Li, Nora Chiang, Betty Tai, Charles K. Marschke, and Richard L. Hawks*

Comparison of Immunoassays for Semiquantitative Measurement of Benzoylecgonine in Urine . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 287
*Rodger L. Foltz, Christine Botelho, Scott A. Reuschel, David J. Kuntz, David E. Moody, and Gloria M. Bristow*

Appendix I: Workshop Summary Outcome Measures and Success Criteria . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 303
*Betty Tai*

Appendix II: Workshop Summary Clinical Decision Tree for Cocaine Addiction Pharmacotherapy . . . . . . . . . . . . . . . . . . . . . . . . 312
*Betty Tai, Charles V. Grudzinskas, Peter Bridge, and Nora Chiang*

# PREFACE

*Betty Tai, Charles V. Grudzinskas, Nora Chiang, and Peter Bridge*

More than 23 million Americans have used cocaine at some time in their lives, and more than 1.3 million are current cocaine users. Cocaine abuse and dependence affect all segments of society with devastating personal, social, and public health consequences. Unfortunately, effective cocaine pharmacotherapies are lacking. Accordingly, the National Institute on Drug Abuse (NIDA) has made the development of an anticocaine medication its number one priority.

More than 30 marketed medications have been tested in the last decade for their effectiveness to treat cocaine addiction. Several review articles (see Elinore F. McCance's chapter, this volume) were published and general conclusions are: (1) most of the open trials had positive results; however, when the studies were repeated in a blinded manner, the results became negative, which leaves the development potential of these medications unclear; (2) the clinical research efforts were primarily focused on the evaluation of a broad range of the marketed medications in the absence of reliable animal and/or clinical models to predict clinical utility; and (3) the heterogeneity across study design coupled with the lack of standardization of methodology used by the researchers in conducting these clinical studies made it impossible to evaluate and compare results for different studies to determine which medications should be advanced for further clinical evaluation.

One classical example of the lack of methodology standards can be illustrated with the review of studies of desipramine, a tricyclic antidepressant that has been widely prescribed to treat cocaine dependence (Halikas et al. 1991). More than a dozen clinical studies have been conducted and published since 1982. A meta-analysis of the published trials was attempted (Levine and Lehman 1991). This task proved to be extremely difficult because of the heterogeneity in the design of the various studies. Some of the subjects who were studied were primarily cocaine abusers, some were methadone maintained, and others were dually diagnosed. The inclusion/exclusion criteria were very different for each study. Regarding dose regimens, the more recent studies provided blood levels instead of doses. The protocol designs included random/nonrandom, open/blind, and controlled/uncontrolled study designs. In general, five categories of outcome measures have been commonly used: psychiatric outcome measures, craving, subjective drug effects, pattern of drug use, and retention in treatment. However, in these published studies, the definitions of outcome measures varied; the instruments and methods used in collecting the outcome measures varied; the questions asked, the adjectives used in forming these questions, and the scales used to assess the subjective effects varied; the sources and frequency for monitoring drug use patterns varied; and the ways the data were analyzed and expressed also varied. These factors made it very difficult to interpret the study results and reach conclusions about whether desipramine is or is not efficacious in treating cocaine addiction.

In light of this, in 1992 the Medications Development Division (MDD) of NIDA proposed the establishment of a Clinical Decision Network, the objective of which was to create an alignment of opinion leaders in academia, government, and the pharmaceutical industry to address issues pertinent to conducting successful anticocaine clinical efficacy trials. The specific goals for this Network were to: (1) ensure that initial pharmacologic activity studies generated information that would be useful in predicting future clinical efficacy, (2) develop common outcome measures and consistent definitions of trial success so that comparison across studies could be made, and (3) create a Clinical Decision Tree to accelerate the development of treatment medications for cocaine addiction.

A series of workshops have been conducted since 1992 to identify and resolve the practical problems confronting researchers in conducting cocaine medication efficacy trials.

- MDD Workshop I (4/20/92)

  Identified the elements missing in the current clinical trial paradigm and Task Forces appointed. Summary was reported in the College on Problems of Drug Dependence (CPDD) (Tai 1992).

- MDD Workshop II (10/18/92)

  Reviewed Task Force Proposals on outcome measures and success criteria. Summary report published by MDD. (See appendix I.)

- MDD Workshop III (11/13/92)

  Reviewed Task Force Proposals on Clinical Decision Tree. Summary report presented at CPDD in 1993. (See appendix II.)

Workshop results were summarized and disseminated at 1992 and 1993 CPDD annual meetings and at the 1992 American College of Clinical Pharmacology (ACCP) annual meeting. The culmination of the effort of these workshops resulted in a NIDA Technical Review meeting "Medications Development for the Treatment of Cocaine Dependence: Issues in Clinical Efficacy Trials," which was held in October 1994 at NIDA. The presentations at this Technical Review were arranged into three sessions. The first session provided an overview of the rationale for pharmacotherapeutical approaches and a comprehensive review of the compounds tested in the past 5 years. The second session targeted issues critical to the design, implementation, analysis, and interpretation of clinical efficacy trials for anticocaine addiction medications. The third and final session focused on a thorough investigation of the limitations and effectiveness of using qualitative and quantitative urinalysis, which is one of the core outcome measures to assess cocaine use in the clinical trials.

This monograph presents the proceedings of the October 1994 Technical Review. It is the editors' hope that this monograph will stimulate further research in the area of development and application of more sensitive clinical trial methodologies for drug abuse research, i.e.: (a) sensitive outcome measures (surrogate or direct) that effectively measure medical improvement in short treatment periods, (b) valid and reliable instruments to measure the above-mentioned outcome measures, (c) animal and/or human pharmacological models that are sensitive for predicting clinical relevance of testing compounds, (d) impact of interaction with levels of psychosocial support, and (e) the inclusion and exclusion criteria of subpatient populations with comorbidity and polysubstance abuse and how they affect the trial designs.

With sensitive methods and standardized processes, future trials may be compared meaningfully and allow valid, critical development decisions to be made to accelerate the identification, evaluation, and development of anticocaine addiction medications.

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# Goals and Rationale for Pharmacotherapeutic Approach in Treating Cocaine Dependence: Insights From Basic and Clinical Research

*Mary Jeanne Kreek*

The early research conducted in the author's laboratory from 1975 onward stemmed from the even earlier work, beginning in 1964 when the author was a member of the laboratory of Professor Vincent P. Dole at the Rockefeller Institute for Biomedical Research (now the Rockefeller University) (Dole et al. 1966; Kreek 1972, 1973*a*; Kreek et al. 1972). At that time, scientists were challenged to develop a treatment for opiate dependency, a problem that is still being addressed, but for which there are now three different pharmacotherapeutic approaches approved by the Food and Drug Administration (FDA), and a fourth under investigation. This chapter will review briefly some of the early concepts because they are relevant for the current major problem: developing a new medication (and possibly a variety of medications) for treating cocaine dependency.

In 1964, researchers had recognized the need to develop a pharmacotherapy for the treatment of opiate dependency, because the most humane and excellent drug-free approaches were not effective for the majority of patients. It must be emphasized from the outset that any pharmacotherapy for managing any addictive disease must be carried out in concert with excellent psychosocial interventions, with counseling and rehabilitation efforts. The very complex disorders of any one of the addictive diseases can only infrequently be managed with chemotherapy alone. Researchers have to be as realistic with respect to cocaine dependency, as they were 30 years ago with respect to opiate dependency. It should be remembered that even the very best "drug free" psychosocial and rehabilitation approaches alone have been successful for extended periods of time in only a limited number of persons, and have been far too limited to accept these as the only approaches available for treatment. Ultimately, what is needed in most cases of both opiate and cocaine addiction is combination therapy. This chapter, however, will be limited to pharmacotherapy.

Several recent studies, including the high school student and household surveys, have elucidated the current magnitude of the cocaine problem. It is estimated that around 24 million people in the United States have used cocaine at some time; over 3 million are occasional cocaine users; about 1.3 million are current cocaine users, and at least 600,000, and maybe many more, are very frequent users, defined as multiple uses each week, either by "binge" pattern or a regular daily use pattern (Kreek 1996). It should be asked, "For which one of these groups are researchers seeking to develop pharmacotherapy?" This is a question that has not been addressed as potential medications for treatment have been identified and clinical trials for treatment of cocaine addiction have been conducted. Researchers have failed to ask, "For whom is this particular medication targeted?" or more generally, "For what group of persons afflicted with chemical dependency problems, of what type, severity and duration?" These questions are critical. If a nicotine patch is used on someone who smokes only 1 cigarette a day, the investigator or clinician may be dealing with a very different situation, and thus outcome, than when investigating, or attempting to treat someone who smokes 10 cigarettes or 3 packs of cigarettes a day. Results may be different because the neurobiology, as well as the behaviors, are different. Researchers need to develop operational definitions and guidelines, such as in 1964 when the author and her colleagues were forced, over a brief period of time, to define opiate addiction. The original operational definition was multiple daily doses of opiate use, usually heroin, with the development of tolerance, physical dependence, and drug-seeking behavior, and a duration of that pattern of behavior for 3 years or more. In a stepwise manner, with the advice of the author's group and many others, the official definition of "3 years" has been, as of 1983, reduced to 1 year of that pattern of behavior, and thus defined the duration of addiction. The Institute of Medicine has published recommendations on the regulations governing methadone treatment (Rettig and Yarmolinsky 1994); the FDA and the Drug Enforcement Agency (DEA) may be considering the available information supporting the concept that even 1 year of daily illicit opiate use may be too long to demand for entry into a pharmacotherapy using an opioid agonist or, alternatively, partial agonist, such as methadone, l-alpha-acetylmethadyl (LAAM), or in the future, possibly buprenorphine (Rettig and Yarmolinsky 1994). The 3-, then 2-, and now 1-year length of addiction requirement is based on the operational definition first formulated in 1964. It still is an operational, not a medical or neurobiological definition, but it has served clinical scientists, clinicians, and policymakers very well because groups of subjects can be compared with respect to their response to treatment, as well as their neurobiology status. There is a definite need now to define different levels of cocaine dependency at an operational level, which will understandably be imperfect biologically, but at least will allow for more effective comparison of clinical and fundamental studies.

If researchers believed that cocaine dependency was solely a behavior that occurs in a social and environmental context, with no neurobiological ramifications, that is, with both no possible predisposition on a genetic basis, and/or with no persistent or permanent alterations of physiology as a result of its use, then no one would discuss the need for development of a pharmacotherapeutic agent. However, irrespective of the hypotheses that may be formulated and addressed, most agree that there are probably either genetic factors that confer or augment vulnerability to develop each of the specific addictions, and/or persistent or permanent changes effected by the drug of abuse, which may contribute to, or cause, the acquisition and perpetuation of the drug-seeking behavior and also the persistence of "drug hunger" or craving, with the proclivity for relapse. Especially important for cocaine addiction is the profound craving associated with the cocaine-abstinent state. However, any genetic or neurobiological factors must be considered in a contextual setting, including: the individual's stage of development, what other kinds of exposures there have been (including both diseases and drugs), and the individual's response to stressors. Also important is the overall environment, and especially the set and setting of drug exposures and related economic factors.

The goals and rationale for the development of a pharmacotherapy for addictions have evolved in the author's laboratory over the past 20 years, based in part on early conceptualizations 30 years ago with respect to opiate dependency and, more recently, with respect to both cocaine dependency and alcoholism (Dole et al. 1966; Kreek 1972, 1973*a*, 1973*c*, 1978, 1991, 1992*a*, 1992*b*, 1992*c*; Kreek and Hartman 1982).

First, an agent must prevent any physiologically based withdrawal symptoms (Kreek 1992*c*). This is especially important with opiate dependency, though possibly of lesser importance with respect to cocaine dependency. However, there are dramatic histories and presentations in the literature of cocaine withdrawal symptoms, especially in the outpatient setting, where cues and other conditioned factors may play a dominant role. In a quiet, stress-minimized inpatient setting, such as that of the clinical research group at the Addiction Research Center, which is the intramural program of the National

Institute on Drug Abuse (NIDA) and the author's laboratory at the Rockefeller University resource at the NIH-supported General Clinical Research Center (GCRC) of the Rockefeller University Hospital, as well as in other clinical investigators' settings, only modest to absent withdrawal symptoms have been described in recently abstinent cocaine addicts (Cambor et al. 1992; Ho et al. 1992).

Secondly, a pharmacotherapeutic agonist needs to reduce drug craving or "hunger." For cocaine dependency, this goal has to be at the top of the list. Long after the cocaine "binge" is over and the cocaine has cleared the body and the major benzoylecgonine (BE) and the other metabolites are gone, craving still persists (Kreek 1992*c*). In fact, relapse may be seen at very distant timepoints and, although cues and conditioning play a role, cravings have arisen in very sterile settings such as a clinical inpatient research unit.

The third goal of any specific pharmacotherapy is normalization of physiological functions disrupted by drug use. Functions that have been disrupted may be epiphenomena. However, it is important to note that some of the disruptions are of the stress-responsive axis, which has been hypothesized to contribute to the perpetuation of drug-seeking behavior.

Finally, any medication ideally should be targeted to a specific site of action, a receptor, or a physiological system, which has been affected or deranged by the drug of abuse in a very specific manner. Therefore, it is imperative that it is clear what the drugs of abuse do, where they act, what the actions are, and what the immediate as well as distant ramifications are, on a biological and neurobiological basis.

After recruitment as a resident in internal medicine at New York Hospital Cornell Medical Center in the autumn of 1963 by Professor Vincent P. Dole, the author had the opportunity to do a research elective at the Rockefeller Institute for Biomedical Research and in early 1964, to join Professor Dole and the late Dr. Marie Nyswander, who also arrived at that time, in the initial research efforts to address the following question: Could a pharmacotherapy for opiate dependency be developed? Some of the criteria for a research pharmacotherapeutic agent then and now are: (1) ideally, the medication should be orally effective; (2) there should be a slow onset of action of that medication to eliminate any reinforcing effects of the agent, so it would not become a primary drug of abuse; and (3) the drug should be long-acting with a gradual offset, as well as onset, of action.

Methadone, which at that time had been studied to a very limited extent, and used in few resources for the "detoxification" of heroin addicts, met all three of these criteria. In 1964, there were no analytical techniques to measure sensitively and specifically any opiate in blood or even in urine; thus clinical observations had to be used to assess the pharmacology of a potential research treatment agent, based on the observed pharmacodynamics. In addition, at that time, a medication was sought that could be given in doses that would not cause euphoria or any other kind of opiate effect. This was achieved with methadone. However, in some early research studies, when doses of methadone were given that exceeded the degree of tolerance developed by the individuals, although true euphoria was not observed, somnolence and sleepiness occurred. If a dose of methadone was selected initially to be less than that for which tolerance has been developed by the individual, no euphoria, no sleepiness, and no other narcotic-like effects would be detected. The dose then could be ascended slowly to achieve ultimately a dose that provides not only tolerance, but cross-tolerance to other opiate drugs. Through the mechanism of cross-tolerance the effects of any superimposed short-acting opiates are "blockaded" (Dole et al. 1966). Finally, a medication should prevent withdrawal symptoms. This may be of lesser importance with respect to the management of cocaine dependency since in a controlled, stress-minimized environment such as a hospital or clinical research unit, withdrawal symptoms following cessation of cocaine use are minimal (Cambor et al. 1992; Ho et al. 1992). However, each one of these characteristics must be sought in the development of pharmacotherapeutic agents for the management of cocaine dependency. Also, for cocaine dependency, like the case of opiate dependency, where it has been clearly desirable to have more than one therapeutic agent, it would be desirable to have several pharmacotherapeutic agents with different actions and mechanisms of action to manage the diverse populations needing treatment.

By 1972, two groups then working independently (now both part of the NIH-NIDA Research Center) developed techniques for measuring plasma levels of methadone, using gas-liquid chromatography (Dole and Kreek 1973; Inturrisi and Verebely 1972, 1973; Kreek 1973*b*, Kreek et al. 1976). Researchers found precisely what was observed clinically, that is, after a single oral dose of methadone during chronic steady-dose treatment, there is a sustained plasma level over a 24-hour dosing interval (Inturrisi and Verebely 1973; Kreek 1973*b*). Secondly, the rise to peak level is gradual, with a resultant gradual onset of action; the peak levels do not occur until 2 to 4 hours after the oral dose is given. The peak plasma levels are very modest, barely a doubling of the nadir. With this slow rate of rise and low peak levels, thus the very slow onset of action, no reinforcing effects or narcotic-like effects are expected, if the proper dose has been administered. From a kinetic standpoint, whereas heroin has a half-life in humans of 1 to 2 hours, and the major morphine metabolite of heroin is 4 to 6 hours, methadone has a half-life of 24 hours in man (Inturrisi and Verebely 1972, 1973; Kreek 1973*b*). Using stable isotope techniques to label both the active and inactive enantiomer of methadone with different amounts of deuterium at specific nonmetabolically reactive sites, the author and her colleagues were able to define, using chemical ionization mass spectrometry, that the half-life of the active l-enantiomer was 48 hours (Hachey et al. 1977; Kreek et al. 1979; Nakamura et al. 1982). This long-acting profile of methadone occurs uniquely in humans. In rodents, methadone has a half-life of about 60 to 90 minutes, similar to that of morphine (Kreek 1979). Thus, the pharmacokinetic profile would have been able to be elucidated only in humans, where it would be ultimately determined.

In good treatment programs, steady and adequate doses of methadone are used, 60 to 120 mg/d for the average patient, after slow escalation from initial lower doses, followed by stabilization of dose (Dole et al. 1966; Kreek 1991, 1992*a*, 1992*b*, 1992*c*). Use of stabilized doses in treatment is critical. One should never use changes in methadone dosage to effect a behavioral change, or use dose changes in a contingency contract for behavior modification. Doses must be kept constant. Otherwise, the rationale and proven mechanism of methadone action as used in appropriate pharmacotherapy is impaired and the desired normalization of disrupted physiology is not achieved. In good programs, there should also be concomitant rehabilitation efforts, psychosocial support systems, and access to medical and psychiatric care. Also, in good programs that combine adequate and stable doses of methadone combined with other psychosocial, counseling, and medical services, retention in 1964 and retention in 1994 (as in the two clinics connected with the NIDA Research Center) ranges from 70 percent to 85 percent, and, after the first 6 months of stabilization in treatment, continuing use of heroin drops to below 15 percent. The actions of methadone prevent withdrawal symptoms and also prevent "drug hunger" or craving, that is, the desire to use other illicit opiates (Dole et al. 1966; Kreek 1991, 1992*a*, 1992*b*, 1992*c*; Rettig and Yarmolinsky 1994). However, the blockade of the euphorogenic or other narcotic-like effects of any superimposed short-acting opiates that is achieved by adequate steady-dose methadone treatment also means that, when on methadone, a patient who tries to get a euphoric or "high" sensation from illicit heroin cannot do so unless extraordinarily large and expensive amounts of heroin are used. In the author's original titration studies, over $200 equivalent of illicit heroin purchased on the streets of New York administered intravenously in a single dose was needed to override the cross-tolerance developed by a full blockading treatment dose, i.e., 60 to 120 mg/day of methadone (Dole et al. 1966).

For any pharmacotherapy to be developed for treatment of cocaine addiction, it may be essential both to block the acute reinforcing and euphorogenic effects of cocaine, and also reduce or eliminate the chronic and persistent craving for cocaine which leads to relapse. It may or may not be found that a single pharmacotherapeutic agent can effect both of these desired effects, since there is evidence from the author's laboratory that more than one neurobiological mechanism may be involved (Branch et al. 1992; Kreek 1987; Maggos et al. 1995; Maisonneuve and Kreek 1994; Maisonneuve et al. 1995; Spangler et al. 1993*a*, 1993*b*, 1994, 1995; Unterwald et al. 1992, 1993, 1994*a*, 1994*b*).

It was also seen that during chronic long-term methadone maintenance treatment, when a stable moderate to high dose of methadone was used, there was normalization of several physiological functions that were critical for normal survival functions as well as for generalized well-being, including behavioral and emotional status, which were functions that were disrupted by chronic use of heroin. Normalization of the stress-responsive hypothalamic-pituitary-gonadal axis, and also normalization of the hypothalamic-pituitary-adrenal axis involved in reproductive behaviors and biology, occur during chronic steady-dose treatment (Cushman and Kreek 1974*a*; Kennedy et al. 1990; Kosten et al. 1987, 1992; Kreek 1972, 1973*a*, 1978, 1992*c*; Kreek and Hartman 1982; Kreek et al. 1981, 1983, 1984*a*, 1984*b*). A moderate extent of normalization to prolactin responsivity occurs, although there is still responsivity of prolactin release as reflected by peak levels of prolactin at the time of peak plasma levels of methadone. However, prolactin levels above normal are not reached (Kreek 1978).

Linked in part to normalization of neuroendocrine function, normalization of immune function indices also occurs during chronic long-term methadone treatment, including normalization of natural killer cell activity, absolute numbers of T cells, T-cell subsets, B cells, and NK cells and, when studied after stabilization for 10 years or more, near normalization of levels of immunoglobulins IgG and IgM, which are profoundly elevated in untreated street heroin addicts (Kreek 1973*a*, 1978, 1994; Kreek et al. 1972; Novick et al. 1989; Ochshorn-Adelson et al. 1994; Ochshorn et al. 1990). Natural killer-cell activity is reduced to a potentially clinically significant level in untreated heroin addicts. This is probably due to multiple factors, including injection of multiple foreign substances and other diseases, but also possibly to indirect or direct opiate effects. It is less clear why there are increased absolute numbers of T cells and B cells in untreated heroin addicts when HIV infection is not present, but that has been a reproducible finding from many studies (Novick et al. 1989; Ochshorn et al. 1990; Ochshorn-Adelson et al. 1994).

By using appropriate doses of methadone, an effective methadone program also prevents drug craving and thus prevents use of dirty needles to inject illicit drugs. When the author carried out a study in which sera that were prospectively banked from 1969 onward from all research subjects entering basic and clinical research in the laboratory were unbanked and studied in 1983-84, HIV was detectable when the AIDS epidemic appeared in the parenteral-drug-abusing population in New York City (DesJarlais et al. 1984, 1989; Kreek et al. 1990; Novick et al. 1986*a*, 1986*b*). This also allowed the author's group to ask about the impact of effective methadone treatment on acquisition of HIV-1 infection. In the Centers for Disease Control (CDC) Bulletin published in the summer of 1984, the author and her colleagues reported that effective methadone treatment prevents HIV-1 infection by reducing or eliminating use of unsterile needles (DesJarlais et al. 1984). Ten years later, there are still waiting lists for entry into methadone maintenance treatment in many regions, and no access to treatment in many other areas. Also over the past 10 years, the unit funding for each treatment resource has gone down, resulting in too few effective or "good" programs, which by definition, use adequate and stable doses of methadone, and also provide ready access to onsite counseling, medical, and psychiatric care. Whatever efficacious medication for treatment of cocaine dependency might be developed, if there are no appropriate treatment resources in which to deliver it, that is, programs that can combine pharmacotherapy with support services in a proper environment, there will never be a therapy that will be effective and generally accepted by patients and by the community. Researchers must address the need for proper access to treatment and form appropriate, effective programs, while developing new medications and conducting exciting and potentially important neurobiological studies.

In addition to methadone, other medications have been developed for treatment of chronic opiate addiction. A longer-acting congener of methadone, which like methadone is a pure opioid agonist directed at the mu opioid receptor LAAM (for which NIDA is to be credited for gaining prompt FDA approval) is now available for maintenance treatment. Buprenorphine, a partial agonist, or mixed antagonist, is currently under study. Naltrexone, a pure opioid antagonist, was approved by the FDA several years ago. Each medication may be beneficial for some heroin addicts, yet each will require administration by appropriately trained staff and with appropriate monitoring of all patients in treatment, as well as initial administration in a treatment modality that will also provide counseling, rehabilitation efforts, AIDS risk reduction, education, and access to medical and psychiatric care, especially for addicts first entering treatment.

In the "worst" or most limited in terms of ancillary services, of all programs reported, in a controlled study that administered an adequate dose of methadone (often not done in minimal services clinics), as reported by McLellan and O'Brien in their "three levels of treatment study," it was found that giving out methadone alone has a 45 to 55 percent success rate in terms of stopping illicit opiate use in unselected heroin addicts (McLellan et al. 1993). In contrast, naltrexone, in unselected heroin addicts (not small groups of physicians or nurse addicts or special groups such as those on probation with a 6-month contract), in the best of studies, including the pivotal multicenter trial planned by the National Academy of Sciences group, has been shown to have effectiveness only in 15 percent to 20 percent of patients and then only for a very short time. This low level of effectiveness resulted in stopping this multicenter trial much earlier than planned (National Research Council Committee on Clinical Evaluation of Narcotic Antagonists 1978). Also, drug-free treatment, in the best of approaches and the worst of approaches, results in only 15 to 30 percent success, measured by retention and remaining in an abstinent state for 1 year or more (Cooper et al. 1983).

Clearly, a pharmacotherapy for cocaine as well as for opiate and alcohol addiction is needed, but it should be appropriately delivered in well-staffed and broad services programs, as discussed earlier. Also needed is a definition of cocaine dependency in terms of different stages of duration and severity so that data analogous to the abundant data on treatment of opiate addiction can be presented. Opiate addiction as defined for criteria for entry into methadone maintenance and LAAM treatment, and thus for all studies discussed here is, is at least 1 year of multiple daily dose uses of heroin, with the development of tolerance, physical dependence, and drug-seeking behavior. Studies have yet to be performed on drug abusers with less than 1 year of daily or intermittent heroin use, of the efficacy of naltrexone, for whom naltrexone is the only pharmacotherapy, by law, that can be used. Also necessary are natural history studies on early drug abusers with opiate dependency for less than 1 year, i.e., short-term addicts. Similarly, 1 year of daily or at least weekly "binge pattern" cocaine use might provide a satisfactory definition for long term or "hard-core" cocaine addicts. Researchers could then target a pharmacotherapy for such a long-term or "hard-core" group and correlate data from treatment outcome studies across centers. At the same time, researchers could develop an intervention for cocaine abusers with a shorter history of use.

The author's laboratory has worked on the hypothesis that the endogenous opioid system may be involved to some extent, and possibly to a considerable extent, in each of three major addictive diseases: opiate, cocaine, and alcohol addictions. The endogenous opioid system has three classes of endogenous opioid peptides: the endorphins, the enkephalins, and the dynorphins. Single genes code for each of these three classes of endogenous peptides. These genes have been cloned, and the biochemical characterization of the several opioid and nonopioid peptides from the single precursor peptide, as well as some of the mechanisms for processing and biotransforming the parent peptides to those various peptides, has been defined. In December 1992, the first opioid receptor gene, the delta opioid receptor gene, was cloned independently by Evans and by Kieffer (Evans et al. 1992; Kieffer et al. 1992). This was soon followed by cloning of both the mu and kappa receptors by Yu, and the mu receptor gene by Uhl, Akil, and Watson, and others (Chen et al. 1993*a*, 1993*b*; Thompson et al. 1993; Wang et al. 1993, 1994*a*, 1994*b*). At this time it seems that there are indeed three genes coding for three types of opioid receptors, as had been predicted through many cell biological and medicinal chemistry studies using primarily selectively synthetic ligands. To date, no separate genes to explain subtypes of each of these three types of opioid receptors, as defined by use of selective chemical ligands, have been found. There is a fourth (or more) "orphan" opioid receptor-like gene(s), with significant homology to the opioid receptor gene, the natural ligand(s), which is still to be determined.

Cocaine acts primarily by inhibiting the synaptic reuptake of dopamine (DA) into presynaptic sites and also inhibits the receptors of serotonin and norepinephrine by acting at their transporters. Of those three neurotransmitters, most studies have focused primarily on DA, since DA has been so closely linked, by many studies in animal models and at the human level, with the reinforcing or the pleasurable effects of drugs of abuse (Koob 1992). DA, normally released into the synapse, primarily acts at postsynaptic DA receptors, now defined as existing in five distinct types with different and opposing effects. DA thereby activates one or more signal transduction systems, including receptor-specific stimulating or inhibiting effects on adenylyl cyclase activity. Similarly, serotonin and norepinephrine released from presynaptic sites may act at many specific receptors with subsequent signal transduction. These neurotransmitters are subsequently transported first back into presynaptic areas by their specific transporter proteins and then back into presynaptic vesicles. There are also presynaptic DA autoreceptors, where DA may act to regulate DA release.

Although the major effect of cocaine that is known is the direct effect of blocking reuptake of the three neurotransmitters at the site of their specific transporters, this effect is transient (Maisonneuve and Kreek 1994; Maisonneuve et al. 1995). Researchers have raised the question of what may be the indirect effects of cocaine on the endogenous opioid peptides and their receptor systems. These may be longer lasting effects, and/or may provide memory that leads to continual self-administration or relapse to drug use. The reinforcing or reward effects of drugs of abuse, the "pleasurable" or "desirable" effects, are thought to be those that lead to "craving" or "drug hunger," resulting ultimately with spontaneous activity, or work, for drug acquisition and drug self-administration. The primary sites of action of drugs of abuse with respect to their "reward" or reinforcing effects have been identified by many groups as being in specific brain regions, all rich in dopaminergic (DArgic) nerve terminals or alternative cell bodies, including primarily the mesolimbic and mesocortical dopaminergic systems, especially the nucleus accumbens, which receives terminals from the ventral tegmental area. Also, some of the locomotor activity effects of cocaine and other drugs of abuse derive from effects on DA projections from the substantia nigra to the caudate putamen region as well as the mesolimbic-mesocortical system effects. In addition, it has been hypothesized that the hypothalamus may be important with respect to modulating, in part possibly through different DArgic pathways located therein that may, in turn, affect the responsivity of related hormone systems (Kreek 1996). At these sites, altered stress responsivity may be localized which, since 1972, the author had hypothesized may be part of the neurobiological basis of addictive disorders (Kreek 1972, 1992*c*). The question is what are the linkages between the DArgic system and the opioid system within these single brain regions, and what are the feedback loops between these regions. Specifically one of the questions the author has been addressing is whether or not dynorphin plays a significant role in the feedback control of DArgic tone (Chou et al. 1994*a*, 1994*b*; Kreek et al. 1994; Spangler et al. 1993*a*, 1993*b*, 1994, 1995, 1996).

Also especially interesting is the role of the stress-responsive axis in the addictive diseases. A single gene and gene product, pro-opiomelanocortin (POMC), yields beta-endorphin, an endogenous opioid, in equimolar concentrations with ACTH, long appreciated as the major stress-responsive peptide in mammals, which causes release from the adrenal cortex of glucocorticoids (cortisol in man, corticosterone in rats). Glucocorticoids, in turn, are critical hormones modulating many metabolic and immune functions. Corticotropin-releasing factor (CRF) is released from the hypothalamus and acts on the anterior pituitary to cause production and release of beta-endorphin and ACTH from POMC. Glucocorticoid released from the adrenal cortex act at glucocorticoid receptors both in the hypothalamus and in the anterior pituitary to affect the negative feedback control of CRF and POMC release was reconfirmed as also regulating these hormones encoding mRNA of rat POMC (Zhou et al. 1996*a,* 1996*b*).

The author's work on opiate dependency has shown in humans that opiates will suppress this hypothalamic pituitary adrenal (HPA) axis acutely; in rodents, however, opiates apparently acutely activate hormones of the HPA axis. When used on a chronic basis in man, short-acting opiates, such as heroin, continue to cause suppression of this HPA axis. However, in an opioid-tolerant and opioid-dependent human being who stops all opiate use and thus goes into opiate withdrawal, the opposite is seen—profound activation of this HPA axis (Kreek 1972, 1973*a,* 1973*c;* 1978, 1992*c*). Some data from the author's group, and from ongoing collaborative work with a group at Yale, support that this opioid activation of the HPA axis may actually precede the first measurable or significant signs and symptoms of opiate withdrawal (Culpepper-Morgan and Kreek, in press; Culpepper-Morgan et al. 1992; Rosen et al. 1995, 1996). Opioid antagonists given to opioid-naive individuals, or to former heroin addicts for management of addiction, exert effects on the HPA axis similar to those found in opiate withdrawal

(Kosten et al. 1986*a*, 1986*b;*Kreek et al. 1984*b*). They cause activation of the HPA axis with release of ACTH, beta-endorphin, and cortisol. During chronic steady-dose treatment with the long-acting opioid agonist methadone, normalization of this axis occurs with normal plasma levels of hormones and normal release, as well as circadian patterns of release of the HPA axis hormones and normal negative feedback control of that release (Kennedy et al. 1990; Kreek 1972, 1973*a*, 1973*c*, 1978, 1992*c*; Kreek and Hartman 1982; Kreek et al. 1981, 1983, 1984*a*).

A provocative test of chemically induced stress using metyrapone, which blocks the last step of cortisol production in the adrenal cortex, blocks the negative feedback control mechanisms by cortisol at the hypothalamic and anterior pituitary sites and thereby normally yields a twofold to fourfold increase in plasma levels of ACTH and beta-endorphin. It has been used by the author's laboratory to study the responsiveness of the HPA axes in former addicts and addicts in treatment. In active heroin addicts taking heroin, a hyporesponsivity to this blockade of cortisol synthesis is seen; in drug-free former heroin addicts, hyperresponsivity to this chemically induced stress is frequently seen (Cushman and Kreek 1974*b*; Kreek 1972, 1973*a*, 1973*c*, 1978, 1987, 1992*c*; Kreek and Hartman 1982; Kreek et al. 1984*a*). In long-term methadone maintained patients, euresponsivity is seen (Kennedy et al. 1990; Kreek 1973*a,* 1973*c*), 1978, 1992*c*; Kreek et al. 1984*a*).

Cocaine has been shown by several laboratories to activate the HPA axis when cocaine is present, both in animal studies and in humans. Very intriguingly, a hyperresponsivity to this chemically induced stress has been found in some, but not all, recently abstinent cocaine addicts. The author has recently studied cocaine addicts with long-term and very heavy usage, using the Addiction Severity Index (ASI) to assess the degree of severity, those who have been cocaine addicts for more than 1 year and have a "binge" and/or daily pattern of cocaine use with sustained social disruption, as well as profound weight loss. When such deeply impaired cocaine addicts were admitted to a research unit following continued "refeeding," very rapid weight gain was observed not unexpectedly (Cambor et al. 1992; Ho et al. 1992). However, no dramatic changes in heart rate or blood pressure were found. In ongoing studies of such patients in an NIH-GCRC unit, hyperresponsivity to metyrapone-induced stress in some subjects was seen. The author is continuing to study this phenomenon in such subjects and also has looked at craving in these subjects using two different visual analog scales, "craving now" and "craving sometime during the last 24 hours."

Three different patterns of responses have been observed: those who have craving at admission and persisting through 21 days in the hospital; those who had craving when they were first admitted but with the craving gradually decreasing and in some cases disappearing; and those with no craving in the stress-minimized environment with no "cues" until, with no apparent provocation, it suddenly emerges again (Cambor et al. 1992; Ho et al. 1992).

A much less expensive and more easily performed technique for quantitatively measuring BE in urine using a commercialized type of immune assay that can be performed quantitatively has been modified from the vigorous work of Batki, Jones, and colleagues, using gas chromatography (Batki et al. 1993; Peters et al., in press; Reid et al. 1995). This method provides much more pertinent information than simply getting a "positive-negative" result from such testing by immune assays, which only indicate that more or less than 300 ng/mL of BE is present in urine. Studies have been conducted in cocaine addicts admitted to the author's Rockefeller University clinical research ward and studied in the early abstinent state for more than 40 days as inpatients, with no passes allowed. After patients have been in the research unit for an extended time, usually more than 40 days, a limited number of authorized passes are allowed. There are twenty 24-hour urines collected in the hospital daily on all study subjects at all times for a variety of measurements. In a 24-hour urine collection, the authors were able to measure and calculate the total BE metabolite excreted each day as well as the absolute concentration per milliliter. Also, both creatinine concentration and the total amounts of creatinine excreted each 24-hour period were determined. During the first few days of hospitalization, the levels of benzoylcognine slowly declined, but remained above 300 ng/mL for several days (Peters et al., in press; Reid et al. 1995). Thus if the standard method of designating urine "positive" or "negative" were used, a specimen collected for monitoring purposes could be incorrectly evaluated as "positive." A steady decline in levels of BE (or the ratio to creatinine) documents no further, or more recent, cocaine use. Conversely, an increase in metabolite levels shows recent further use, thus "relapse," with the implied interpretation being continuing or relapse to cocaine use. Like the Batki and Jones group, the author's group has proposed and demonstrated that expressing quantitative data, from both spot urine collections made in the clinic, as well as 24-hour urine collections made in an inpatient research setting, as a ratio of BE to creatinine, may rectify any false-negative data that could result from purposeful or accidental dilution of urine (Batki et al. 1993;

Peters et al., in press). Any illicit use of cocaine while out on pass in this group study, which occurred in three study subjects only, was found by the reappearance of BE in the urine after the initial steady decrease and then disappearance of metabolite. The magnitude of the levels of benzylecgonine would reflect the amount of cocaine used.

Several years ago, in the author's laboratory, a rat model was developed to mimic human patterns of cocaine use. Whether daily or weekly, cocaine is most often self-administered in a "binge" pattern, with multiple doses given over a usually 1- to 24-hour timeframe, although sometimes much longer, and then with no cocaine used for a period of time. In animal models, cocaine was administered just before what would be the sleep time in rats, again parallel to the frequent time of human "binge" use by the cocaine addict. In this model, repeated doses of cocaine are given at 9:30, 10:30, and 11:30 in the morning (Branch et al. 1992). Then no cocaine is administered for the next 22 hours. A variety of behavioral, neurochemical, cellular, and molecular biological measurements are made. Food intake was found to be similar in both low dose (2.5 mg/kg, three times per day) and high dose (10 mg/kg, three times per day) cocaine-treated and saline-treated animals. Weight gain, however, was different. An initial slowing of weight gain was found in the late adolescent/early adult rats; the weight gain then became equivalent after 7 to 10 days of cocaine administration.

Locomotor activity monitoring is conducted in the author's laboratory on individual animals in homecages on a 24-hour basis. On day 1 of "binge" pattern cocaine administration, locomotor activity is increased after each of the three administrations of cocaine (15 mg/kg three times per day) (Unterwald et al. 1994*b*). By the last days of 14 days of "binge" pattern cocaine administration, a profound difference is seen in locomotor activity in cocaine-treated versus saline-treated animals. This is "sensitization" described and studied by many other workers, but using very different experimental protocols. In this study, a regular, although intermittent, "binge" pattern of chronic cocaine administration with a 22-hour interval between cocaine doses caused a hypersensitivity to cocaine with respect to its effects on locomotor activity (Unterwald et al. 1994*b*). Since in this study, 24-hour activity in homecage was measured with no removal of animals for cocaine/saline injections, and no removal for behavioral measurement, the timecourse of development of sensitization has been determined, which seems to be an extraordinarily robust phenomena in rat models. Both acutely and when studied in a chronic basis, this locomotor activation exactly parallels the increases in extracellular fluid concentrations of DA measured directly in microdialysis studies conducted using the same treatment protocol (Maisonneuve and Kreek 1994; Maisonneuve et al. 1995; Unterwald et al. 1994*b*).

Microdialysis studies were performed with probes in the nucleus accumbens (ventromedial striatum) and in the caudate putamen (dorsolateral striatum) (Maisonneuve and Kreek 1994; Maisonneuve et al. 1995). It was found that following each dose of cocaine, levels of DA in the extracellular fluid are elevated. However, following the second and third dose of cocaine on the first day of cocaine administration, a plateau of the rises in DA concentration in extracellular fluid is seen. In contrast, when actual levels of cocaine in the caudate putamen are measured, it was found that the half-life of cocaine in this brain region is around 30 minutes; thus the amounts of cocaine accumulate, with further increases in cocaine levels in the brain regions after each of these three "binge pattern" cocaine administrations (Maisonneuve and Kreek 1994). Thus there is evidence for acute adaptation or tolerance to this particular effect of cocaine on extracellular DA concentrations on this first day of cocaine administration.

After 14 days, there is again a rise in DA levels in the extracellular fluid after each dose of cocaine, paralleling the behavioral data on locomotor activity (Maisonneuve et al. 1995). However, two interesting issues were noted. At every timepoint the actual concentrations of DA in the extracellular fluid in both the caudate putamen and nucleus accumbens regions are lower in the animals that had been receiving the "binge" pattern cocaine administered on a chronic basis, as contrasted to saline-treated animals receiving cocaine for the first time on the last day of the study. Much of the microdialysis study data published by various research groups are presented as percent changes from baseline values. In the author's studies, in which all probes used are precalibrated, the data could also be measured in actual amounts of DA. Significant reductions of extracellular fluid concentrations of DA, both prior to and following each injection of cocaine, were found on the final 14th day of "binge pattern" cocaine administration. If these data were then expressed in the more conventional units of percent change from baseline, essentially the same responses were observed after the first doses of cocaine in both cocaine and saline-pretreated animals. However, no plateau in DA levels was observed after the second and third cocaine doses in the chronic cocaine-treated rats. This relatively greater rise in extracellular fluid DA after chronic cocaine administration would parallel what was seen with the cocaine-induced activity, which is an enhanced response to the chronic intermittent cocaine administration or sensitization (Maisonneuve et al. 1995).

In related studies using the technique of quantitative autoradiography, the effects of this "binge" pattern cocaine administration on altering $D_1$ and $D_2$ DA receptor densities were demonstrated (Unterwald et al. 1994*b*). The $D_2$ type DA receptors were increased in density significantly at 7 days after "binge" cocaine administration in three areas of the mesolimbic-mesocortical system, including the nucleus accumbens, the caudate putamen, and olfactory tubercle. These changes, however, were transient. By 14 days, no alterations in the density of $D_2$ DA receptors were found in any brain region (Unterwald et al. 1994*b*). However, $D_1$-type DA receptors were found to be significantly increased after 14 days in both the nucleus accumbens and the olfactory tubercle. This enhanced density of $D_1$ DA receptors following chronic "binge pattern" cocaine administration occurred specifically in areas of the brain known to be involved in the rewarding effects of cocaine and other drugs of abuse. These findings are provocative, especially with known linkage between the $D_1$ DA receptors and dynorphinergic neurons.

What is the answer to the question, "What other changes are present after DA levels have returned to normal in the extracellular fluid or, in fact, to modestly suppressed levels, and if there are enhanced $D_1$ DA but not $D_2$ DA receptor densities, what happens to the endogenous opioid system?" What has been found is that the mu opioid receptors are significantly increased in density, as measured by quantitative autoradiography using mu selective opioid ligands in the caudate putamen, the nucleus accumbens, the cingulate cortex, and also in the basolateral amygdala after 14 days of "binge pattern" cocaine administration (Unterwald et al. 1992, 1994*a*).

The effects of "binge" pattern cocaine administration on kappa type opioid receptors have also been studied (Unterwald et al. 1994*a*). Again, when using selective ligands, significant increase in binding capacity in the caudate putamen, the nucleus accumbens, the cingulate cortex and also in the olfactory tubercle, again all brain regions that are part of the mesolimbic, mesocortical, or nigrostriatal DArgic system, where DArgic terminals are abundant as projections from the substantia nigra and the ventral tegmental area, have been found. No significant changes in mu or kappa opioid receptors were found within other brain regions where they are equally or more dense in the basal state. It is of special interest that the significant changes in $D_1$ DA receptor density and in kappa receptor density were both found in two areas of central importance for reward mechanisms:  the nucleus accumbens and the olfactory tubercle, both important regions of the mesolimbic-mesocortical DArgic system. These findings are of special importance since dynorphinergic activity is known to be linked to activation of the $D_1$ type DA receptors (Spangler et al., in press-*a, -b, -c*; Unterwald et al. 1994*b*) and since full-length dynorphin peptides are the natural ligands of the kappa opioid receptors. It has been hypothesized that dynorphin acts to lower DArgic tone, with negative feedback control from the caudate putamen to the substantia nigral site of DArgic neurons, which project to the caudate putamen and which are part of the nigrostriatal DArgic system, and also possibly from the nucleus accumbens to the ventral tegmental area site of DArgic neurons, which project to the nucleus accumbens, amygdala, olfactory tubercle, cingulate cortex, and other brain regions of the mesolimbic-mesocortical-DArgic system.  The authors also have hypothesized that there may be action of dynorphinergic peptides to decrease DArgic tone directly within the caudate putamen and within the nucleus accumbens. This hypothesis is supported by the recent finding of DAT (DA transporter) gene message expression within both the caudate putamen and the nucleus accumbens (Maggos et al. 1995, in press).

Several scientists at the NIH-NIDA Research Center have developed a modified technique of solution hybridization RNase protection assay, in which 18S ribosomal RNA is used as an internal standard, and both sense and antisense riboprobes are used to construct calibration curves of internal standards and gene of interest (Branch et al. 1992; Inturrisi et al. 1988).  Following gel analysis of hybridization with the use of each new probe or experimental perturbation, the routine procedure for quantitative measurements of the levels of mRNA of genes of interest in specific brain regions of individual animals includes precipitation with trichloracetic acid of hybridized species, followed by filtration and counting.  This modified procedure has allowed the study of specific brain regions from individual animals with precise measurements that allow detection of the small, but potentially very significant, changes that impact or perturb integrated physiology in mammalian physiology . (Spangler et al. 1993*a*, 1993*b*, 1994, 1995, 1996; in press-*a, -b*, -*c*). Using this technique, researchers use ribosomes, usually subcloned from probes provided by various colleagues for studies of specific genes from specific species.  The author prefers using riboprobes that are over 500 bases in length to increase stringency of the solution hybridization RNase, protection assays, a sharp contrast to the very short probes that must be used for in situ hybridization, which usually are 150 to 250 bases in length.

It has been seen that at the end of 14 days of "binge pattern" cocaine administration, there is no change in gene expression, measured as quantities of mRNA levels of the DA transporter gene expression in the substantia nigra or in the ventral tegmental areas, the two areas where this gene is the most highly expressed (Maggos et al. 1995, in press).

Recently, the author used probes for rat genes cloned by Yu and Uhl, and others, following the initial identification of cDNAs of the mouse delta opioid receptor by expression cloning, achieved by Evans and by Kieffer and colleagues, to study the quantitative levels of gene expression of the kappa and mu opioid receptor in specific brain areas (Chen et al. 1993*a*, 1993*b*; Evans et al. 1992; Kieffer et al. 1992; Wang et al. 1993). Researchers are continuing studies to look at the impact that drugs of abuse and treatment agents on these opioid receptors, as well as on signal transduction systems related to these receptors. High levels of abundance of gene expression for both the mu and kappa receptors have been found in the caudate putamen and the nucleus accumbens, and also in the hypothalamus as well as in the substantia nigra, the olfactory tubercle, and the amygdala (Spangler et al. 1994, 1995). The author also has remapped, using this very sensitive technique, the levels of gene expression of opioid peptide genes in various regions (Branch et al. 1992; Spangler et al. 1993*a*, 1993*b*, 1996, in press-*a*, -*b*). Again, the two regions of great abundance of proenkephalin and prodynorphin gene expression are the nucleus accumbens and the caudate putamen, and to a lesser extent the hypothalamus.

The author then studied the effects of binge pattern cocaine administration on opioid peptide gene expression. After 14 days of "binge" cocaine administration, no changes in proenkephalin gene expression were observed in any brain region (Branch et al. 1992). However, following that pattern of chronic cocaine administration in the rat, significant upregulation of prodynorphin mRNA levels in caudate putamen were found (Spangler et al. 1993*a*, 1993*b*).

It has been hypothesized that dynorphin A, one of the major opioid peptides processed from the initial single gene product of prodynorphin gene expression, may act directly or indirectly to lower DArgic tone (Kreek et al. 1994). In humans, DA plays a dominant role in tonically inhibiting prolactin release, acting on the tuberoinfundibular DArgic system. Such an effect may parallel the effect of dynorphin on the mesolimbic, mesocortical, and nigrostriatal DArgic systems. Thus, an elevation in prolactin levels may reflect a selective or general reduction in DArgic tone on the brain. The question is whether dynorphin A will effect an increase in prolactin levels in humans. Dynorphin A normally has 17 amino acids; the truncated form of dynorphin A (1-13) of natural sequence has been made available to the author for independent clinical research in humans by Neurobiological Technologies, Inc., in Richmond, California. With Dr. B. Chait, Head of the Laboratory of Extended Range Mass Spectrometry, at Rockefeller University, a matrix-assisted, laser desorption mass spectrometry method has been developed to study neuropeptide processing and biotransformation (Chou et al. 1993*a,* 1993*b,* 1993*c*, 1994*a*, 1994*b*, in press; Yu et al., in press). Using this technique, all of the specific products of neuropeptide biotransformation ex vivo can be analyzed simultaneously. By this technique, it has been determined that the most abundant active opioid component of dynorphin A (1-13) is dynorphin A (1-12), along with the nonopioid peptides dynorphin A (2-12), which may have some different activities, and dynorphin A (4-12) (Chou et al. 1993*a*, 1993*b*, 1994*a*, 1994*b*, in press). It has been found that both the opioid peptides dynorphin A (1-13), dynorphin A (1-17), and dynorphin A (1-6), and also the major nonopioid biotransformation products dynorphin A (2-17) and dynorphin A (2-12), inhibit adenylyl cyclase in rat caudate putamen membranes (Claye et al. 1996). In pilot studies, when dynorphin A (1-13) is given to normal volunteers, it causes a significant rise in serum prolactin levels, which persists for around 90 minutes when 120 $\mu$g/kg of dynorphin A (1-13) is given intravenously (Kreek et al. 1994). This is dose-responsive effect, with further increases and more prolonged elevations in serum prolactin levels when 500 $\mu$g/kg of dynorphin A (1-13) is administered intravenously. Controlled studies in patients with defined addictive diseases are continuing.

In summary, there are at least two medications, methadone and LAAM, both specific opioid agonists, an additional partial agonist under study, buprenorphine, that are highly efficacious in the treatment of opiate addiction, and also, an antagonist, naltrexone, effective in small, well-defined subpopulations. All of these are directed at the opiate system, not surprisingly. But much more surprising, and now well elucidated by the author's group and supported by findings from other groups, is that cocaine disrupts specific aspects of the endogenous opioid system in humans as well as in animal models. Thus, in theory, there may be some pharmacotherapeutic benefit from targeting an opioid agonist or partial agonist in cocaine dependency, at least in the setting of codependency with an opiate such as heroin. Several studies, most recently by Borg and colleagues (1995), have shown that although some 70 to 90 percent of former heroin addicts have used cocaine heavily prior to admission to methadone maintenance, over 40 to 50 percent stop using cocaine during effective methadone maintenance treatment, and only 20 to 30 percent continue with regular cocaine (Borg et al. 1995). This is an effect that can be attributed primarily to the positive psychosocial intervention; however, it may, in part, be attributable to pharmacological actions of methadone or LAAM or buprenorphine (Borg et al. 1995).

Several groups including that of Volpicelli and O'Brien at the University of Pennsylvania and O'Malley and colleagues at Yale, as well as B. Mason at the University of Miami have shown that specific opiate antagonists such as naltrexone or nalmefene may be useful in the treatment of alcoholism (Mason et al. 1994; O'Malley et al. 1992; Volpicelli et al. 1992). Thus there is increasing evidence that the endogenous opiate systems, as well as the DArgic system, and possibly also the serotonergic system, may be intrinsically involved in each of these three major addictions: heroin, cocaine and alcohol. All of these neurobiological and clinical findings should guide researchers in the exploration for a pharmacotherapy for cocaine addicts.

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# Overview of Potential Treatment Medications for Cocaine Dependence

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## INTRODUCTION

The search for a pharmacotherapeutic agent for the treatment of cocaine dependence began in the early 1980s as clinicians and researchers realized that the cocaine epidemic was growing rapidly and that standard drug counseling and self-help groups made little impact on the addiction for many cocaine abusers. Cocaine was initially viewed as a recreational drug for the wealthy with limited negative consequences for the majority of users (Grinspoon and Bakalar 1980). The widespread availability of cocaine and increased prevalence of more addictive routes of administration (intravenous (IV) and smoked) have resulted in cocaine abuse and dependence becoming one of the most serious public health problems in the United States. The National Institute on Drug Abuse (NIDA) estimates that at least 2 million persons are cocaine abusers and that 1 to 3 million persons are in need of treatment (Kozel and Adams 1985).

Cocaine dependence is different from other major mental and substance use disorders in that intensive research efforts have only been underway for about 15 years. Truly elegant work has provided at least a partial explanation for cocaine-induced behavioral and physiological effects, and epidemiological and treatment research to date has elucidated many of the clinical challenges yet to be met. The lag between an understanding of molecular, cellular, and neurobiological effects of cocaine and their relationship to behavioral responses induced by cocaine has resulted in the testing of pharmacological agents aimed at impacting cocaine abuse based on rationales limited by the scientific and clinical understanding of the disease at that time. The evolution of clinical trials methodologies that will yield more useful clinical information and effectively test underlying hypotheses continues. The gaps in scientists' knowledge and limits in clinical methodology to date have restricted the clinical application of many studies. Given these limitations, it is not surprising that no widely efficacious pharmacotherapy for the treatment of cocaine dependence has emerged thus far.

This chapter will summarize the most recent efforts to identify an effective medication for the treatment of cocaine dependence with a focus on work reported over the last 5 years. Some of the clinical attributes for development of an ideal pharmacotherapy will be discussed, as well as rationales utilized for selecting potential pharmacotherapies. New possibilities for medication treatment of cocaine dependence will be briefly reviewed. These may constitute the rudiments of hypotheses and rationales for effective treatments in the future for this most difficult and challenging disorder.

## RATIONALE FOR PHARMACOTHERAPY OF COCAINE DEPENDENCE

Pharmacotherapy of any substance use disorder should be undertaken to address specific problems arising in the course of treatment. For example, the use of medication is often necessary to treat withdrawal syndromes, particularly those in which patients are physiologically addicted to the substance. The choice of a pharmacotherapy for withdrawal should be based on a medical assessment that considers the patient's past and present medical history, as well as consideration of the past history of detoxification and the level(s) of care available. Medication is also considered as a means of relieving craving, especially early in abstinence when such urges put the patient at significant risk for relapse. Effective anticraving medications for most substances of abuse are not available at this time, with the one major exception of methadone maintenance for opiate dependence. Medication treatment may be considered for the initiation and maintenance of abstinence from the substance of abuse. There are limited examples of such medications for the treatment of addictive diseases at this time, including methadone and other long-acting opiates such as buprenorphine or l-alpha-acetylmethadyl (LAAM), which induce tolerance to the effects of opiates. Naltrexone is useful for the treatment of opiate dependence by preventing euphoria when opiates are self-administered. Disulfiram (Antabuse), a drug that results in an aversive physical reaction when alcohol is taken, is a useful adjunct in the treatment of alcohol dependence for selected patients.

Cocaine does not cause physiological dependence, but the psychological addiction in patients with cocaine use disorders can be disabling (Gawin and Ellinwood 1988, 1989). An abstinence syndrome has been described for cocaine dependence and consists of three phases: the "crash," withdrawal, and extinction (Gawin and Kleber 1986, 1988).

Medication management of these phases could be useful for the treatment of cocaine use disorders.

The "crash" is associated with exhaustion following a binge, but other symptoms may occur including agitation, anxiety, depression, and psychosis. These symptoms may require emergent medical and psychiatric evaluation and treatment. An important part of the management of patients with such symptoms is a thorough psychiatric evaluation. Patients in whom symptoms of agitation, psychosis, or depression do not abate over the first few days of treatment, or those in whom such symptoms worsen, may have a comorbid psychiatric disorder that requires psychiatric care. This distinction is critically important in cocaine abusers. Several investigators have shown that comorbid psychiatric disorders occur at high frequency in cocaine abusers (Rounsaville et al. 1991; Weiss and Mirin 1986; Weiss et al. 1988). Further, the lack of appropriate psychiatric care will have a significant negative impact on the patient's ability to initiate and maintain abstinence. Finally, these patients have needs that are not adequately addressed in standard cocaine abuse treatment, which decreases the likelihood that treatment outcome in these patients will be positive. Such individuals require dual diagnosis treatment, which can address both the cocaine abuse and the psychiatric disorder (Hellerstein and Meehan 1987; Martino et al. 1995; Roberts et al. 1992).

The cocaine withdrawal syndrome is a constellation of affective and psychological symptoms lasting from 2 to 10 weeks and is marked by decreased energy, lack of interest, and anhedonia. These symptoms fluctuate and are not severe enough to meet diagnostic criteria for an affective disorder. Symptoms do not occur uniformly in newly abstinent cocaine abusers and, in particular, patients who are hospitalized following cessation of cocaine use may not experience substantial withdrawal symptoms (Brower et al. 1988; Weddington et al. 1990). The cocaine withdrawal syndrome does not generally require medical treatment or pharmacotherapy. However, it is during this time that relapse risk is greatest, so that development of a pharmacotherapy that could assist the patient in initiating and maintaining abstinence would be of great utility in the treatment of cocaine dependence.

## DEVELOPMENT OF A PHARMACOTHERAPY FOR COCAINE DEPENDENCE

In developing an effective pharmacotherapy for substance dependence, the various actions of the drug must be identified. Those effects that will decrease substance abuse should be targeted for pharmacotherapy development. In the case of cocaine, there are several effects that may be points for pharmacotherapy intervention. Cocaine dependence is characterized by either daily or binge use of the drug, perpetuated by intense craving that use of the drug induces (Jaffe et al. 1989). An agent that decreases cocaine craving would be useful for treatment of cocaine dependence. Craving is stimulated by the euphoria induced by the drug (the cocaine "high"). A drug that also could diminish cocaine "high" might assist patients in maintaining sobriety. Finally, repeated use of cocaine is associated with dysphoria, paranoia, and agitation. Development of a medication treatment that could accentuate these adverse psychological effects after a single use might also dissuade the cocaine abuser from using subsequent doses of cocaine.

The development of a medication for treatment of cocaine dependence should include consideration of what the "ideal" properties of such a pharmacotherapeutic agent might be. These attributes are summarized in table 1. A medication should be available by a convenient route of administration. Oral preparations are most frequently used and are accepted by patients and clinicians. A preparation that provides for a long-acting medication treatment, such as an intramuscular (depot) formulation, or a transdermal preparation, would offer certain advantages, including a decrease in medication noncompliance and less frequent medication doses. While frequent clinic visits are desirable early in treatment when it is important to engage the patient and assist in the induction of abstinence, frequent visits are less important in later stages of treatment when the patient has been able to utilize treatment effectively and could, in some cases, impede the patient's ability to engage in employment and other activities important to the recovery process.

Medications must be medically safe and have few side effects. Patients must be willing to accept the medication as an important and useful part of treatment for their cocaine dependence. It is important to match patients to treatments. There will be patients who will embrace philosophies of drug abuse treatment that discourage the use of

**TABLE 1.** *Properties of an ideal pharmacotherapy for cocaine dependence.*

- Convenient route of administration: oral, intramuscular (depot formulation), or transdermal.
- Long acting.
- Medically safe with few side effects.
- Acceptable to patients presenting for treatment.
- Ideally, little abuse liability.
- Useful for more than one class of drug since many cocaine abusers are polysubstance abusers.
- Used in conjunction with behavioral treatments that target the drug abuse and psychosocial problems related to the drug abuse.

medication treatments and rely on group support and internal motivation (such as self-help organizations). Other patients may have comorbid psychiatric disorders that would be more appropriately treated with standard psychotropic medications indicated for the psychiatric disorder. Some patients will have medical disorders that would make them poor candidates for a medication treatment of their drug abuse (e.g., disulfiram would be contraindicated in the alcoholic patient with esophageal varices, and caution must be used in naltrexone treatment of an opiate-dependent individual with hepatic impairment). Finally, stage of treatment for the cocaine addiction must be considered. Pharmacotherapies will be most useful in the withdrawal phase when relapse risk is greatest. It would be unusual to initiate medication for cocaine dependence after several months of sustained abstinence.

An ideal medication treatment for cocaine dependence would have little abuse liability and would be useful for treatment of other addictions in addition to cocaine. Cocaine abusers are often polysubstance abusers and frequently require treatment for alcoholism or opiate abuse/dependence. Marijuana is also a frequently abused drug. At this time, no drug has been shown to be efficacious for treatment of polysubstance abuse, though some promising results have been shown for naltrexone for opiates (Fraser 1990; Ling and Wesson 1990), alcohol (O'Malley et al.

1992; Volpicelli et al. 1992), and disulfiram (for cocaine and alcohol) (Carroll et al. 1993; Van Etten et al. 1994). Finally, any medication treatment must be utilized in conjunction with psychosocial therapies to maximize clinical benefit to the cocaine-dependent patient.

### Pharmacotherapy Approaches

Medications development for cocaine dependence has followed two basic approaches. The first has been an attempt to identify drugs that function as cocaine antagonists, and the second has been to develop drugs with properties similar to cocaine but with a longer duration of action, e.g., cocaine analogs. Cocaine antagonists include drugs that attenuate the acute reinforcement and other effects that have become associated with cocaine use. Advantages to the use of cocaine antagonists are that decreasing euphoric effects of cocaine may be helpful in terminating the abuse of the drug and in enhancing compliance with treatment. Another advantage would be the low abuse liability of these drugs. A problem with the use of cocaine antagonists is that such drugs might produce dysphoria in patients, since the hedonic (and reinforcing) effects of cocaine are thought to be mediated through dopaminergic systems (Fibiger et al. 1992; Koob 1992). Drugs that block the hedonic effects of cocaine could block hedonic effects in general, resulting in dysphoria. Cocaine analogs include drugs that would indirectly block acute cocaine effects by inducing cross-tolerance. Advantages of such drugs include a reduction in cocaine abstinence or withdrawal symptoms and enhanced compliance due to the mood-enhancing effects of the drug. This might assist the patient in breaking the cycle of cocaine use and could be helpful in the treatment engagement process. A problem with this approach could be that cocaine analogs would be stimulant drugs with abuse liability and street value. Stimulant drugs may increase craving for cocaine or possibly increase cocaine use. The use of such drugs would require careful monitoring in an outpatient setting.

## PHARMACOTHERAPY FOR COCAINE DEPENDENCE—RECENT RESEARCH

The epidemic of cocaine abuse has resulted in intensive efforts to develop effective treatments. These efforts include development of both psychosocial interventions and medication treatments for cocaine dependence. The purpose of this chapter is to review developments in the search for an effective pharmacotherapy for cocaine dependence. This chapter will also briefly consider additional agents that have yet to be examined, but serve as examples of approaches that represent the rationale of the use of cocaine agonists (medications that share some pharmacological properties of cocaine) and the use of cocaine antagonists (drugs that, based on pharmacological properties, might antagonize cocaine effects) for the treatment of cocaine addiction.

A large number of medications have been used for treatment of cocaine dependence (table 2). These medications have been utilized for a variety of cocaine-related effects, including treatment of cocaine withdrawal, treatment for cocaine craving, and initiation and maintenance of abstinence. Many of these medications have appeared to be promising in open trials. However, once studied in randomized, placebo-controlled clinical trials, no medications to date have been shown to have substantial efficacy for the treatment of cocaine dependence.

In addition to the lack of strong evidence for efficacy, there have been numerous problems in the interpretation of results from many studies. These difficulties are summarized in table 3. Studies to date have often included small sample sizes and have been hampered by large dropout rates. Diagnostic criteria have varied across clinical trials (some studies enroll patients meeting diagnostic criteria for cocaine dependence, others cocaine abuse, and others do not specify patient diagnosis). It is difficult to know whether the results of a study are generalizable to the population of treatment-seeking, cocaine-addicted individuals. Many of the larger studies have looked at pharmacotherapies for cocaine dependence in patients with primary opiate dependence and who receive methadone maintenance. While this population tends to be more available for followup because of the need to report to a clinic daily for methadone treatment, it is likely that these patients are different from patients with primary cocaine use disorders. Therefore, results obtained in studies enrolling methadone-maintained cocaine abusers may not be generalizable, though certainly such studies are important given the prevalence of cocaine abuse in this group. Outcome variables differ among clinical trials making it difficult to determine a drug's effectiveness. Studies that have utilized self-reports without confirmation by urine toxicology screen may not be reflective of cocaine use by study participants.

Future studies should be double blind and placebo controlled, and include large, diagnostically well-defined samples. Standardized outcome variables to assess the efficacy of the medication treatment

**TABLE 2.** *Medications that have been used to treat cocaine abuse.*

**Dopaminergic agents**

bromocriptine
L-dopa
methylphenidate
mazindol
pergolide
amantadine
flupenthixol
haloperidol
bupropion
selegiline
AMPT
benztropine
ritanserin

**Antidepressants**

desipramine (DMI)
fluoxetine
sertraline
imipramine
maprotilene
phenelzine
trazodone
lithium

**Miscellaneous agents**

buprenorphine
carbamazepine
nimodipine
mazindol
nifedipine
disulfiram
clozapine
tyrosine
naltrexone
gepirone
tryptophan
placebo

should be utilized. Regular urine toxicology confirmation of drug use needs to be included in all efficacy trials.

The following sections will summarize recently (primarily the last 3 years, but in some instances up to 5 years) reported studies of pharmacotherapies for cocaine dependence. The summary will include only studies that have been conducted in humans with primary cocaine use disorders (i.e., cocaine abuse or cocaine dependence). Although many studies have been conducted in methadone-maintained, cocaine-abusing patients (i.e., patients with primary opiate dependence), these patients are sufficiently different from primary cocaine-abusing patients both in terms of the neurobiological and physiological effects of the primary drug of abuse and in terms of the clinical treatment that results reported for them may not be generalizable to those with primary

**TABLE 3.** *Difficulties with interpretation of cocaine pharmacotherapy study outcomes.*

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- Outcome variables differ:

    Cocaine self-reports.

    Urine toxicology screens.

Retention in treatment.

Craving assessments.

Length of abstinence.

Depression.

Cocaine withdrawal symptoms.

- Open-label studies.
- Small sample size.
- High dropout rate.
- Diagnosis at entry: Cocaine abuse versus cocaine dependence.
- Severity of cocaine use is usually not considered.
- Many studies report on opiate-dependent cocaine abusers.

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cocaine use disorders. Summaries of the results of preclinical studies will be limited to one very recent report that may have important implications for chronic treatment of humans with the specified agent (haloperidol) and recent preclinical reports that may lead the field in new directions for medication development for cocaine dependence. Finally, the studies reported will include both outpatient clinical trials and inpatient studies that examine the effects of a particular agent on cocaine responses in human volunteers.

## Desipramine

Desipramine (DMI), a tricyclic antidepressant agent, was one of the first medications to be studied as a treatment for cocaine dependence and, as such, is one of the most extensively studied pharmacotherapies for cocaine dependence to date. DMI may act as a specific antianhedonic agent in cocaine-dependent patients (Gawin and Kleber 1986). Several recent controlled clinical trials in cocaine abusers have been reported and are summarized (table 4). One double-blind, placebo-controlled, randomized trial included 29 subjects. In this trial, 14 subjects were randomized to treatment with 40 mg of DMI daily. Outcome variables included cocaine use self-reports, urine toxicology screens, and cocaine craving measures. No significant difference was observed between DMI and placebo treatment in this study (Covi et al. 1993, 1994). A large clinical trial that examined the efficacy of DMI and psychotherapy, alone and in combination, as a treatment for ambulatory cocaine abusers has been reported (Carroll et al. 1994). In this 12-week, double-blind, placebo-controlled trial, 139 subjects were assigned to one of four conditions. These conditions included relapse prevention therapy plus DMI, clinical management plus DMI, relapse prevention plus placebo, and clinical management plus placebo. The mean dose of DMI was 200 mg daily and was adjusted by a nonblinded psychiatrist in response to plasma concentration (target ranges 300 to 750 ng/mL) and side effects. All groups showed significant improvement in treatment retention and a reduction in cocaine use at 12 weeks, but there were no significant main effects for psychotherapy, pharmacotherapy, or the combination. Lower severity patients (cocaine use 1 to 2.5 g/week) had improved abstinence initiation when treated with DMI. DMI was significantly more effective than placebo in reducing cocaine use during the first 6 weeks of treatment. Depressed subjects had a greater reduction in cocaine use than nondepressed subjects and had a better response to relapse prevention therapy. The findings of this study underscore the heterogeneity among cocaine abusers and the need to develop specialized treatments for distinct subgroups of cocaine abusers.

## Dopaminergic Agents

The most widely accepted explanation of cocaine-induced euphoria is that dopamine (DA) reuptake inhibition results in increased extracellular DA concentration in the mesolimbic and mesocortical reward pathways in the brain. Numerous studies have provided evidence for the importance of DA in the reinforcing properties of cocaine. Low doses of DA

**TABLE 4.** *Desipramine (DMI).*

**Desipramine (DMI)**

Rationale: Blocks reuptake of norepinephrine and to a lesser extent dopamine; postulated to act as a specific antianhedonic agent in cocaine-dependent patients.

Controlled studies:

- (Covi et al. 1993, 1994): DMI was not significantly better than placebo.

- (Carroll et al. 1994): DMI may be useful for selected patients: Lower severity patients (cocaine use: 1 to 2.5 g/wk) had significantly longer periods of abstinence.

  DMI was associated with improved abstinence initiation weeks 2 through 6 only.

receptor antagonists, when injected systemically, consistently increase cocaine self-administration in animals, indicating a of blockade of cocaine effects (Koob 1992). In addition, 6-hydroxydopamine (6-OHDA) lesions of dopaminergic terminals in the nucleus accumbens produce extinction-like responding and a reduction in cocaine self-administration (Lyness et al. 1979; Roberts et al. 1977, 1980). Similar lesions in other areas of the brain (frontal cortex and caudate nucleus) do not alter cocaine self-administration (Koob et al. 1987; Martin-Iverson et al. 1986). In vivo brain microdialysis has also provided additional experimental data that indicate that mesolimbic DA levels are associated with cocaine reward (Fibiger et al. 1992). Conversely, cocaine abstinence that is characterized by depression, irritability, and anxiety (the "crash") has been hypothesized to result from dopaminergic hypoactivity (Dackis and Gold 1985). Support for this hypothesis is derived from studies of in vivo microdialysis during cocaine withdrawal (Weiss et al. 1992). These experimental findings support the rationale for use of dopaminergic agents in the treatment of cocaine dependence described below.

## Dopamine Antagonists

DA antagonists, of which two have been examined (haloperidol and flupenthixol), have been postulated to have potential as treatment agents for cocaine dependence. This is due to their ability to block specific DA receptors that might alter cocaine acute effects thought to be mediated by a rapid increase in DA in the nucleus accumbens. The effects of haloperidol on subjective and physiologic responses to cocaine was examined in five cocaine-abusing volunteers (Sherer et al. 1989). In a randomized, double-blind study design each subject received either haloperidol 8 mg or placebo followed 20 minutes later by IV cocaine (40 mg) administration. Haloperidol attenuated expected increases in blood pressure, but not heart rate. Haloperidol reduced subject ratings of pleasant sensation following cocaine administration, but had no effect on cocaine euphoria as measured by the variable "rush" (table 5). Flupenthixol is a thioxanthene with DA antagonist properties. It is being examined in controlled, outpatient trials for efficacy in the treatment of cocaine dependence. In a 6-week, double-blind, placebo-controlled study comparing DMI and flupenthixol, an interim data analysis showed a trend toward better engagement in treatment for patients randomized to flupenthixol treatment (Gawin et al. 1993; Khalsa et al. 1994) (table 5).

**TABLE 5.** *Dopamine (DA) antagonists.*

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Rationale: Cocaine euphoria appears to be mediated by a rapid increase in DA in nucleus accumbens; blockade of specific DA receptors may change acute cocaine effects.

**Haloperidol**

- (Sherer et al. 1989): Pretreatment with haloperidol 8 mg followed by IV cocaine (40 mg) showed decrease in pleasant effects of cocaine, but no effect on cocaine euphoria as measured by "rush."

- (Kosten et al. 1994): Chronic haloperidol treatment enhanced cocaine-induced conditioned place preference (CPP), while acute treatment blocks CPP.

**Flupenthixol**

- (Gawin et al. 1993; Khalsa et al. 1994): A 6-week, double-blind, placebo-controlled study comparing DMI and flupenthixol in cocaine-dependent outpatients showed a trend toward better engagement in treatment in group assigned to flupenthixol.

The effect of both acute and chronic haloperidol treatment on cocaine-conditioned place preference in rats has been recently studied (Kosten et al. 1994). Using a full cocaine dose-response function, acute haloperidol was shown to block cocaine-conditioned place preference. In contrast, chronic haloperidol treatment resulted in behavioral supersensitivity, lowering the dose of cocaine that supports conditioned place preference. This finding supports those of other studies that show that chronic haloperidol treatment leads to receptor supersensitivity and enhanced locomotor responses to cocaine (LeDuc and Mittleman 1993). This study indicated that haloperidol and similar DA antagonists might be contraindicated for long-term treatment of cocaine abuse. It appears that one possibility is that such agents could contribute to enhanced cocaine effects. These findings may also help to partially explain the high prevalence of cocaine abuse in neuroleptic-maintained schizophrenics (Schneier and Siris 1987).

## Dopamine Agonists

It has been postulated that chronic cocaine use may deplete central DA, which could result in supersensitivity of dopaminergic receptors. DA hypofunction induced by cocaine abuse may underlie craving and withdrawal symptoms often observed in recently abstinent cocaine-dependent patients. The following section includes a review of recent studies that have used agents with DA agonist properties in the treatment of cocaine use disorders.

Bromocriptine is an agonist with high affinity for the $D_2$ receptor. Treatment with bromocriptine might reverse dopaminergic deficits induced by cocaine and ameliorate craving and withdrawal. Two studies have addressed the utility of bromocriptine in the treatment of cocaine dependence by examining effects of pretreatment with bromocriptine on cocaine administration (table 6). Pretreatment with either bromocriptine 2.5 mg or 5 mg 2 hours prior to cocaine administration had no effect on cocaine euphoria; however, heart rate following bromocriptine pretreatment was augmented (Kumor et al. 1989). Another study examined the effects of bromocriptine pretreatment (0, 1.2, or 2.5 mg) on IV cocaine (0, 12.5, 25, or 50 mg) administration. While bromocriptine did not alter the subjective effects of cocaine, significant increases in heart rate were again observed with the combination (Preston et al. 1992).

Controlled outpatient clinical trials have been limited with bromocriptine. Early open studies using doses of 1.25 mg to 2.5 mg daily have yielded

**TABLE 6.** *Dopamine (DA) agonists.*

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Rationale: Cocaine may deplete central DA, which may result in DA receptor supersensitivity and DA hypofunction, which may underlie craving, withdrawal.

**Bromocriptine ($D_2$ agonist)**

- (Sherer et al. 1989): Bromocriptine pretreatment (2.5 mg or 5 mg) 2 hours prior to cocaine administration; no effect on cocaine euphoria, increase in heart rate.
- (Preston et al. 1992): Pretreatment with bromocriptine (0, 1.2, 2.5 mg) did not alter subjective effects of cocaine (0, 12.5, 25, 50 mg IV); significant increase in heart rate was observed with the combination.
- Few controlled clinical trials.
- Reports of difficulty with adverse event profile (headache, vertigo, syncope).

**Amantadine (DA release)**

- (Sholar et al. 1994): Acute effects of amantadine (0, 200 mg, or 400 mg) on intranasal (IN) cocaine administration; attenuation of heart rate increases following cocaine administration for both doses of amantadine; the 200 mg dose was associated with decreased cocaine "high," chronic amantadine administration (100 mg twice daily) enhanced euphoric effects of cocaine in male subjects.
- (Weddington et al. 1991): 12-week, single-blind study (N = 54), all treatment groups showed decrease in cocaine use and craving; no evidence for efficacy of amantadine (400 mg/d).
- (Alterman et al. 1992): Amantadine 100 mg twice daily (N = 42) associated with significantly less cocaine-positive urines than placebo-treated patients, though there was no difference in self-report of cocaine or other substance use.

**TABLE 6.** *Dopamine (DA) agonists (continued).*

**Bupropion (inhibits DA uptake)-Bromocriptine ($D_2$ agonist)**

- (Montoya et al. 1994): 8-week open-label trial using combination of bupropion ≤ 300 mg/d and bromocriptine ≤ 7.5 mg/d; no decrease in cocaine-positive urines.

**L-deprenyl (inhibits DA metabolism)**

- (Haberny et al. 1994): Five subjects with history of IV cocaine abuse, 2-day pretreatment with L-deprenyl 10 mg or placebo followed by cocaine (0, 20, 40 mg IV); no alteration of physiological or subjective effects of cocaine by L-deprenyl.

**Methylphenidate (DA release)**

- (Grabowski et al. 1994): Methylphenidate 20 mg SR twice daily + 5 mg standard versus placebo (N = 7) for 8 weeks; decreased craving in methylphenidate group, no decrease in cocaine use.

conflicting results and suffered from high dropout rates (Dackis et al. 1987; Giannini and Baumgartel 1987). In a double-blind clinical trial using bromocriptine 5 mg to 7.5 mg daily, the study drug was poorly tolerated with frequently reported side effects of headaches, vertigo, and/or syncope resulting in high dropout rates (Tennant and Sagherian 1987). The use of bromocriptine to treat acute cocaine abstinence has recently been revisited in a small, double-blind, placebo-controlled trial (Moscovitz et al. 1993). Bromocriptine 1.25 mg three times daily or placebo was given to patients presenting to an emergency room for minor medical complaints, but who were found to be abusing cocaine by urine toxicology screen. Subjects were given followup appointments four times over a 15-day period. Although the small sample size lacked statistical power to make inference, the investigators found that bromocriptine was generally well tolerated. Five of 14 subjects randomized to bromocriptine returned for all visits and three of these subjects had negative urine toxicology screens on all visits. Subjects randomized to bromocriptine and placebo showed no difference in retention (bromocriptine group 43 percent, placebo group 31 percent). Those randomized to bromocriptine had more urine toxicology screens negative for cocaine (67 percent) than those randomized to placebo (31 percent). Drawbacks to this study include the small sample size and its atypical quality, since these were not subjects seeking treatment for perceived problems with cocaine use. Additionally, there was no monitoring to determine compliance with the study medication. Novel treatments with bromocriptine are being explored and could include the use of bromocriptine in combination with other agents. For example, an open-label study of the combination of bromocriptine ($\leq$ 7.5 mg daily) and bupropion ($\leq$ 300 mg daily) was conducted over an 8-week study period (Montoya et al. 1994*a*, 1994*b*). There was a significant reduction in pre- and posttreatment self-reports of cocaine use ($p < 0.01$), but no significant change in urine toxicology screens (both qualitative and quantitative). This study provides evidence for the safety of this combination, but does not support efficacy for the treatment of cocaine dependence. However, these studies indicate that bromocriptine may have some utility in the treatment of cocaine dependence and should be considered in future, well-controlled studies.

Amantadine increases dopaminergic transmission, but whether the mechanism is DA release, direct effects on DA receptors, or DA reuptake blockade is unclear. There have been few recent controlled studies of amantadine for treatment of cocaine dependence. These are summarized in table 6. One study examined the effects of acute amantadine (200 mg or 400 mg) and chronic amantadine (100 mg twice daily for 4 days) followed by insufflation of cocaine 0.9 mg/kg (Sholar et al. 1994). Acute effects of both amantadine doses on cocaine responses included attenuation of heart rate increases, while the amantadine 200 mg dose was associated with a decrease in cocaine "high." Chronic administration of amantadine 100 mg twice daily was associated with increased "high" in male subjects after cocaine administration as compared to female subjects. A 12-week, single-blind comparison of DMI (200 mg daily), amantadine (400 mg daily), or placebo as adjunctive treatments to counseling for cocaine dependence has been reported (Weddington et al. 1991). All treatment groups demonstrated decreased cocaine use, craving, and psychiatric symptoms, indicating no specific treatment effect of the active medication treatments. The effectiveness of amantadine was evaluated in a double-blind, placebo-controlled trial in which 42 patients in a day treatment program were randomized to amantadine 100 mg twice daily ($N = 21$) to be taken over 10 days or placebo ($N = 21$). Urine toxicology screens showed that those who had received amantadine were significantly more likely to be free of cocaine ($p < 0.05$) at the 2-week and 1-month followup visits, though self-reports for the two treatment groups did not differ. This study indicated that amantadine may have some efficacy in early treatment of cocaine dependence (Alterman et al. 1992).

Bupropion is a second-generation antidepressant that enhances dopaminergic transmission, but has little effect on serotonergic neurotransmission. To date, experience with bupropion in clinical trials has been limited. In an open pilot study, six methadone-maintained cocaine abusers participated in an 8-week outpatient study in which they received bupropion 100 mg three times daily (the usual dose used for treatment of depression). At the 8-week followup, only one of the study participants was still using cocaine. At the 3-month followup, the four patients who achieved abstinence from cocaine during bupropion treatment remained free of cocaine use as indicated by self-report and urine analysis (Margolin et al. 1991). The results of a large multicenter study designed to assess the effectiveness of bupropion for treatment of cocaine addiction in methadone-maintained patients showed little evidence for efficacy in this group (Vocci et al. 1994). Another study explored the use of bupropion in conjunction with bromocriptine treatment in primary cocaine abusers (table 6) (Montoya et al. 1994*a*, 1994*b*). Given its DA agonist properties, this drug should be considered for further clinical trials to assess its efficacy for treatment of primary cocaine dependence.

L-deprenyl is a monoamine oxidase type B inhibitor that specifically inhibits the metabolism of DA. Its present indication is for the treatment of Parkinson's disease. The ability of L-deprenyl to potentiate DA has led to consideration of its use in the treatment of cocaine dependence. A study in five human volunteers examined the effects of L-deprenyl alone and in combination with cocaine (Haberny et al. 1994) (table 6). Subjects were treated with L-deprenyl 10 mg or placebo for 2 days. Each subject participated in cocaine administration sessions following treatment with L-deprenyl and following placebo treatment. Cocaine doses of 0, 20, and 40 mg were administered intravenously at 60-minute intervals. No differences in physiological (cardiovascular) parameters or drug liking were observed for sessions that included cocaine-alone administration or the L-deprenyl-cocaine combination.

Methylphenidate (MP) is a stimulant drug primarily used in the treatment of childhood attention deficit hyperactivity disorder. MP is a DA agonist with pharmacological properties that include DA release and reuptake inhibition. It is being studied as an initial treatment for cocaine dependence (Grabowski et al. 1994) (table 6). This study represents a unique approach to drug development for cocaine dependence. Subjects were cocaine-dependent volunteers who were admitted to an inpatient unit for a 2-day period during which pretreatment safety, physiological, behavioral, and cognitive assessments were made. Subjects were monitored and stabilized for 2 weeks in an outpatient clinic. Subjects (N = 7) were then randomly assigned either to placebo or to MP 20 mg (sustained-release preparation) twice daily and 5 mg of standard MP daily in an 8-week trial. Quantitative urine benzoylecgonine (BE) determinations were conducted on urine samples obtained twice a week and patient self-reports were also elicited. A preliminary report from this ongoing study has indicated that retention is good, with only one dropout from the MP group thus far. Reported desire to use cocaine and "preoccupation with use" are decreased in the MP group. Nonsignificant increases in blood pressure and pulse were observed in the MP group. No significant difference in abstinence or cocaine use as determined by quantitative urine BE were observed in this small sample. This study demonstrated a novel approach to drug development and showed that this class of medications may be useful in the treatment of cocaine dependence.

## Cocaine Antagonists

A variety of medications have been examined for their effectiveness in blocking the reinforcing effects of cocaine. These drugs, including mazindol, fluoxetine, carbamazepine, naltrexone, and disulfiram, which have been the subject of study over the past several years, have a broad range of pharmacological properties, and all differ greatly in primary indication. However, all have been postulated to antagonize the effects of cocaine through pharmacological properties specific to each drug, which might alter neurobiological and reinforcing effects of cocaine.

*Mazindol.* The euphorigenic and reinforcing effects of cocaine are thought to be related to the effect of cocaine on DA reuptake inhibition. Although the potency of cocaine-like drugs as inhibitors of DA uptake is highly correlated with reinforcement in animal studies, several potent DA uptake blockers do not produce addiction and are not associated with euphoric effects in humans (Rothman 1990). Mazindol is a DA reuptake inhibitor without abuse liability. As such, mazindol may antagonize the effects of cocaine and be useful in the treatment of cocaine dependence. One study has reported on the effects of cocaine alone and in combination with mazindol in cocaine-abusing volunteers (Preston et al. 1993) (table 7). Subjects participated in a crossover study that included 12 acute drug conditions. Subjects were randomized to treatment with mazindol 0, 1, or 2 mg orally 2 hours prior to administration of IV cocaine (0, 12.5, 25, or 50 mg). Cocaine and mazindol alone were found to significantly

**TABLE 7.** *Cocaine antagonists.*

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**Mazindol**

Rationale: Blocks DA reuptake, may substitute for cocaine, but with weaker effects, less abuse liability, cocaine use during treatment may be less reinforcing.

- (Stine et al. 1992): Mazindol 2 mg daily or placebo (N = 33); no effect on cocaine use, no significant adverse events.
- (Preston et al. 1993): Mazindol pretreatment (0, 1, and 2 mg) followed by cocaine administration (0, 12.5, 25, 50 mg IV), no evidence that mazindol altered subjective effects of cocaine, but the combination significantly increased heart rate and blood pressure.

**Fluoxetine (FLX)**

Rationale: A serotonin (5-HT) reuptake inhibitor; cocaine potently inhibits 5-HT reuptake, which may play a role in the dysphoric effects of cocaine; medications such as FLX may accentuate such effects.

- (Walsh et al. 1992): Double-blind placebo crossover study (N = 5), FLX 30 and 40 mg, decreased response to cocaine 40 mg (IV), no correlation between FLX level and cocaine responses.
- (Walsh et al. 1994*a*): Double-blind placebo crossover study (N = 8), dose ranging FLX 0, 20, 40, 60 mg/d, cocaine 0, 20, 40 mg, FLX 40 mg and 60 mg doses decreased subjective effects of cocaine, no cardiovascular toxicity.
- (Batki et al. 1993): Open treatment with FLX (mean dose = 45 mg/d) for 9 weeks in methadone-maintained, cocaine-dependent patients; quantitative urine BE showed significant decrease in amount of cocaine used by the end of the study.
- (Batki et al. 1993): FLX 40 mg versus placebo (N = 32) in cocaine ("crack")-dependent patients. FLX associated with longer retention (11 weeks versus 3 weeks), but there was no difference in quantitative urine BE.

increase heart rate and blood pressure. Mazindol had mild stimulant effects and cocaine increased ratings for stimulant effects and desire for cocaine. Mazindol followed by cocaine administration was associated with larger and more sustained increases in heart rate and blood pressure as compared to cocaine alone. Mazindol was not found to alter subjective effects of cocaine. One subject had significant increases in heart rate and blood pressure during mazindol-cocaine administration, which continued for 3 hours. This subject also experienced anxiety and paranoia during the mazindol-cocaine condition. One 12-week, double-blind, placebo-controlled clinical trial of mazindol 2 mg daily in cocaine-dependent subjects has been reported (Stine et al. 1992) (table 7). Of 33 patients who consented to participate, 16 dropped out, and the average length of treatment was 5 weeks. Mazindol had no significant association with depression or anxiety symptoms, nor has this dose been associated with any reduction in cocaine use as measured by self-reports and urine toxicology screens.

*Fluoxetine.* Cocaine has been found to inhibit the uptake of serotonin (5-HT) two to four times more potently than that for DA (Ritz and Kuhar 1989). 5-HT synthesis or receptor blockade potentiates (but the 5-HT precursor, 5-hydroxytryptophan, antagonizes) cocaine-induced locomotor activity in animals (Cunningham et al. 1992). Studies have demonstrated that chronic cocaine administration results in a net decrease in 5-HT neurotransmission as a result of enhanced 5-HT autoregulatory mechanisms (Pradhan et al. 1978). This has been postulated to be a mechanism underlying the psychological consequences of chronic cocaine abuse. These findings have led to trials of medications with effects on central serotonergic regulation for the treatment of cocaine abuse. The drug in this class that has been studied most extensively is fluoxetine.

Several well-controlled clinical trials with fluoxetine have been conducted in patients with cocaine use disorders (table 7). One double-blind, placebo-controlled, crossover study (N = 5) determined the effects of treatment with 30 mg or 40 mg of fluoxetine followed by administration of IV cocaine (40 mg). Fluoxetine was associated with decreased “rush,” magnitude of drug effect, drug liking, and “good effects.” There was a negative correlation between response to the cocaine dose and plasma fluoxetine concentration, suggesting greater attenuation of cocaine effects with higher plasma fluoxetine levels (Walsh et al. 1992). A second study has been reported that examined the interaction of cocaine and fluoxetine in a dose-ranging study (N= 8) using fluoxetine 0, 20, 40, or 60 mg daily on an ascending schedule, with cocaine administration 0, 20, or 40 mg intravenously at each fluoxetine dose (Walsh et al. 1994*a*). There was no evidence of cardiovascular toxicity under any of the conditions. The 40 mg and 60 mg doses of fluoxetine were found to decrease subjective effects of cocaine. Fluoxetine has been utilized in outpatient clinical trials in both methadone-maintained, cocaine-dependent patients and in patients with primary cocaine use disorders. An open study in which methadone-maintained, cocaine-dependent patients were treated with a mean dose of fluoxetine 45 mg daily and followed with quantitative plasma and urine cocaine and BE concentrations showed a significant decrease in cocaine use by the end of the 9-week treatment period, though most subjects did not achieve abstinence (Batki et al. 1993). Urine BE concentration has been reported to correlate with patients' self-reports regarding cocaine use and craving (Batki et al. 1992). Fluoxetine has also been used as a treatment for primary cocaine dependence (Washburn et al. 1994). Subjects were randomized to receive fluoxetine 40 mg daily or placebo over a 12-week study period (N = 32). Subjects receiving fluoxetine remained in treatment for a significantly longer period of time (11 weeks versus 3 weeks) and remained abstinent for longer periods. An analysis of two double-blind, placebo-controlled trials in primary cocaine-dependent patients and secondary (methadone-maintained) cocaine-dependent patients showed that fluoxetine increased retention in primary cocaine-dependent outpatients and reduced cocaine use and craving in secondary cocaine dependence (Batki et al. 1994). These findings appear to indicate potential effectiveness of fluoxetine in the treatment of cocaine dependence.

*Carbamazepine*. Carbamazepine (CBZ) is an anticonvulsant medication hypothesized to have potential as a treatment for cocaine abuse because of its ability to block cocaine-induced "kindling" in rodents. Kindling has been postulated to be a model for the neurophysiological basis of cocaine craving. CBZ may also reverse the DA receptor supersensitivity that may result from chronic cocaine use, and its potential as a treatment for cocaine dependence has been examined in several studies (table 8). A double-blind, placebo-controlled, crossover study of the interaction of CBZ with cocaine in six cocaine users has been reported (Hatsukami et al. 1991). In this study, subjects were treated with CBZ 400 mg daily for 5 days, which was followed by administration of one 40 mg dose of smoked cocaine base. No changes in subjective responses to cocaine were observed, but significant increases in heart rate and diastolic blood

**TABLE 8.** *Cocaine antagonists.*

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**Carbamazepine (CBZ)**

Rationale: Blocks cocaine-induced "kindling" in rodents; kindling has been proposed as a neurophysiological mediator of cocaine craving.

- (Hatsukami et al. 1991): Pretreatment of six cocaine users with CBZ 400 mg for 5 days followed by 40 mg smoked dose of cocaine; no change in subjective effects of cocaine; significant increases in heart rate and diastolic blood pressure.

- (Gorelick et al. 1994): CBZ did not alter self-administration of IV cocaine in cocaine-dependent subjects; CBZ levels of 1 to 3 or 4 to 7 $\mu$g/mL.

- (Halikas et al. 1993): CBZ 400 mg versus placebo as adjunct to psychosocial therapy, in sample of 183 cocaine abusers for 12 weeks, significant decrease in cocaine-positive urines and reported reduction in craving; CBZ levels not reported.

- (Montoya et al. 1993): CBZ versus placebo in sample of 62 cocaine-dependent patients for 8 weeks; CBZ levels $5.6 \pm 0.8$ $\mu$g/mL, no significant differences between CBZ and placebo-treated groups.

- (Kranzler and Bauer 1993) CBZ 400 to 600 mg versus placebo in 40 cocaine-dependent patients; no effect of CBZ on any measures (craving, cocaine use, paranoia during cocaine use, urine toxicology).

**Naltrexone**

Rationale: Opioid antagonist; opiate pathways may be involved in some of the reinforcing effects of cocaine; could potentially be blocked by naltrexone administration.

- (Kosten et al. 1992): 50 mg naltrexone or placebo daily for 10 days followed by IV cocaine administration (0.125 to 0.5 mg/kg); "dollar value" of cocaine decreased following naltrexone treatment; augmentation of heart rate but no effect on blood pressure for the naltrexone-cocaine condition.

- (Carroll et al. 1993): Open pilot of disulfiram and naltrexone for cocaine-dependent, alcohol abuse/dependent patients: naltrexone had no effect on cocaine or alcohol use.

- (Walsh et al. 1994*b*): Naltrexone in dose range 3.125 mg to 200 mg (weekly dose increases) had no effect on subjective or physiological effects of IV cocaine (0, 20, 40 mg).

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pressure occurred. In another double-blind, placebo-controlled study that directly examined the safety and efficacy of CBZ in reducing cocaine use and craving, subjects were administered CBZ in dosages that resulted in plasma concentrations of either 1 to 3 mcg/mL (doses of 200 mg daily) or 4 to 7 mcg/mL (doses of 400 mg to 600 mg daily). CBZ did not alter cocaine self-administration or craving in these cocaine-dependent subjects. No evidence for safety problems or toxicity with the combination of cocaine and CBZ was observed in this study (Gorelick et al. 1994).

Several double-blind, placebo-controlled studies in outpatients with cocaine use disorders have been reported. In a 20-day, controlled, fixed-dose (CBZ 200 mg, 400 mg, or placebo) trial, 30 volunteers unmotivated for treatment and whose use of cocaine was unchanged from their usual during the study period were evaluated for cardiovascular effects before and during CBZ treatment. Systolic blood pressure was increased (2.1 mm Hg) and corrected QT intervals on electrocardiogram were shortened, while pulse was significantly increased (2.3 beats/minute), although all observations remained within normal limits throughout the study (Halikas et al. 1991). Several other studies have been conducted to determine the effectiveness of CBZ for the treatment of cocaine use disorders in outpatients. One study was conducted in which 183 subjects meeting diagnostic criteria for cocaine abuse were randomized to CBZ 400 mg or 800 mg daily or placebo as an adjunct to psychosocial therapy. CBZ 400 mg was associated with a significant decrease in cocaine-positive urines and a reduction in cocaine craving, and these findings were negatively correlated with CBZ level (Halikas et al. 1993). Another double-blind, placebo-controlled study that investigated the efficacy and safety of CBZ treatment in 62 subjects meeting diagnostic criteria for cocaine dependence found no significant difference in cocaine use, cocaine-positive urine samples, or depressive symptoms measured by the Beck Depression Inventory. Plasma CBZ levels of 5.6±0.8 mcg/mL were achieved by week 4 of this study (Montoya et al. 1993). Another study examined CBZ 400 mg to 600 mg daily in 40 cocaine-dependent males over a 12-week study period. No significant effect of CBZ was observed for any of the outcome variables, which included self-reports of cocaine use, weekly urine for BE, cocaine craving, frequency or intensity of use, or cocaine-associated paranoia (Kranzler and Bauer 1993).

*Naltrexone*. Naltrexone is an opioid antagonist that has been examined as a treatment agent for cocaine abuse in several small studies to date (table 8). The rationale for use of naltrexone for cocaine addiction is that opiate pathways may be important to pleasurable or euphoric effects of cocaine; an antagonist of this pathway might decrease the reinforcing effects of cocaine and, as a result, decrease cocaine use. This hypothesis is supported by primate studies in which an attenuation of cocaine self-administration was observed during naltrexone treatment (Mello et al. 1991). One study examined the self-reported and cardiovascular effects of intravenously administered cocaine (0.125, 0.25, 0.50 mg/kg) after 10 days of treatment with naltrexone 50 mg or placebo in a double-blind, randomized, within-subjects design (Kosten et al. 1992; Silverman et al. 1993). Cocaine-induced increases in self-reported dollar "value of cocaine" and "unpleasant" were less during naltrexone than placebo administration. Cocaine increased peak heart rate, and this elevation was augmented by naltrexone. Cocaine-induced alterations in blood pressure did not differ across naltrexone and placebo conditions. Another study examined the effects of a range of naltrexone doses (3.125 mg to 200 mg, with weekly dose increases) on the subjective and physiological effects of IV cocaine (0, 20, and 40 mg) (Walsh et al. 1994*b*). In this study, naltrexone had no effect on subjective or physiological responses to cocaine. One open pilot study compared the effectiveness of naltrexone 50 mg daily to that of disulfiram 250 mg daily for treatment of outpatients with cocaine dependence and alcohol abuse (Carroll et al. 1993). Naltrexone did not appear to impact cocaine or alcohol use in this study. Findings thus far with naltrexone indicate that it would be suitable for large, controlled outpatient trials to determine efficacy in the treatment of primary cocaine use disorders.

*Disulfiram*. Disulfiram is an inhibitor of aldehyde dehydrogenase that has been used in the treatment of selected patients with alcohol abuse or dependence. Three pilot studies have examined the efficacy and safety of disulfiram treatment for cocaine dependence (table 9). One recent study in six cocaine-dependent volunteers examined the effect of disulfiram 250 mg on responses to IN cocaine (2 mg/kg) using a randomized double-blind, placebo-controlled design (Hameedi et al. 1995; McCance-Katz et al. 1993). There was no significant difference in cocaine "high" or in physiological responses during disulfiram-cocaine administration as compared to cocaine alone. However, subjects reported decreased craving for cocaine when treated with disulfiram prior to cocaine administration. Additionally, several subjects reported significant dysphoria when disulfiram preceded cocaine administration. Plasma cocaine concentration following disulfiram and cocaine administration was significantly greater, and this may have contributed to the decreased craving and increased dysphoria observed in some subjects.

**TABLE 9.** *Cocaine antagonists.*

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**Disulfiram**

Rationale: Many cocaine abusers are comorbid abusers of alcohol; use of alcohol leads to cocaine use in some persons and alcohol enhances euphoric effects and alleviates dysphoric effects of cocaine; inability to use alcohol with cocaine may decrease cocaine use.

- (Hameedi et al. 1995; McCance-Katz et al. 1993): Double-blind, randomized study of the effect of disulfiram 250 mg on IN cocaine administration (2 mg/kg); no effect on cocaine "high," but decreased craving, increased anxiety and paranoia, no evidence for toxicity based on cardiovascular responses.
- (Carroll et al. 1993): Open pilot study in 18 cocaine-dependent, alcohol-abusing outpatients found disulfiram 250 mg daily was associated with significantly less cocaine and alcohol use as compared to treatment with naltrexone 50 mg daily.
- (Van Etten et al. 1994): Open treatment of outpatients with cocaine dependence and alcohol abuse found a significant decrease in both cocaine (> twofold decrease in cocaine-positive urines) and alcohol use.

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Another study reported on the effects of adjunct disulfiram therapy in outpatients meeting DSM-III-R criteria for cocaine dependence and alcohol abuse (Van Etten et al. 1994). Patients were treated for ≥ 2 weeks on and off disulfiram 250 mg daily. Significantly fewer days of drinking and fewer drinks per occasion were reported during disulfiram treatment. A greater than twofold decrease in cocaine-positive urinalysis results was obtained during disulfiram treatment. An open pilot study has been reported in which 18 outpatients meeting diagnostic criteria for cocaine and alcohol dependence (but not physiologically dependent on alcohol) were randomized to treatment with disulfiram 250 mg daily or naltrexone 50 mg daily in conjunction with individual psychotherapy during a 12-week open trial (Carroll et al. 1993). Primary outcome measures included frequency and intensity of alcohol and cocaine use. Subjects self-reports of substance abuse were collected during weekly interviews with blind raters and verified by urine toxicology screens. Breathalyzer samples were obtained at each visit and all were negative. Subjects treated with disulfiram reported significantly lower alcohol use days as compared to subjects taking naltrexone, fewer total days using alcohol, fewer total drinks during treatment, and more total weeks of abstinence. Cocaine use was also significantly reduced in the disulfiram group, with patients reporting a significantly lower percentage of cocaine use days, fewer days of cocaine use, and fewer observed positive urine screens for cocaine. Subjects reported fewer total grams of cocaine use and more total weeks of abstinence, although these differences were not statistically significant. One explanation for these results was that alcohol may be a powerful conditioned cue for cocaine craving and that disulfiram treatment may reduce exposure to alcohol, thereby arresting the chain of cues leading to cocaine use. In addition, findings from a study of simultaneous cocaine and alcohol administration (McCance-Katz et al. 1993) showed that cocaine abusers can reliably distinguish euphoria associated with combined cocaine-ethanol use from that of cocaine alone and prefer the combination. Disulfiram-maintained cocaine abusers may be less inclined to initiate cocaine use if they know they cannot potentiate cocaine euphoria or titrate negative acute cocaine effects through concurrent alcohol use. These findings indicate that disulfiram may have some efficacy in the treatment of cocaine dependence, but this remains to be confirmed in large, well-controlled outpatient trials.

## FUTURE DIRECTIONS

A variety of drugs are being examined in preclinical studies and early clinical trials to determine their potential as medication treatments for cocaine dependence. These include drugs that might be expected to act as cocaine agonists, such as the DA uptake inhibitors, which have shown some promise in attenuation of cocaine effects in animal studies. Examples of such medications include benztropine (Acri et al. 1994), ifenprodil (Acri et al. 1994), and GBR 12909 (Char et al. 1994; Glowa et al. 1994) (table 10). Medications that might act as cocaine antagonists are also in preclinical and early clinical trials to examine potential safety and efficacy for treatment of cocaine dependence (table 10). One example of such a drug is the 5-$HT_2$ antagonist ritanserin. A single-blind trial conducted with eight cocaine-abusing volunteers pretreated with ritanserin, and who then participated in a cocaine administration study, has been reported (Sullivan et al. 1994). Ritanserin (5 mg and 10 mg) appeared to attenuate cocaine responses. Cocaine antagonist-type drugs might also include atypical neuroleptics such as risperidone or clozapine (Kosten and Nestler 1994) and the $D_1$ antagonist SCH23390 (Heidbreder and Shippenberg 1994). Human studies have been initiated to determine the effects of clozapine pretreatment on cocaine administration (F. Hameedi, personal communication, October 1994). The N-methyl-D-aspartate (NMDA) (excitatory amino acid) antagonists dextrophan and dextromethorphan have also been studied in animals with some evidence for attenuation of expected cocaine effects (Sepinwall et al. 1992).

Although no medication has emerged that effectively treats the cocaine-dependent patient, research to date has yielded important information about the utility of numerous medications in the treatment of this disorder. As important, the work in this field has yielded information that will be critical to the design of future studies that will then provide even greater insights into the treatment of cocaine dependence. Preclinical studies continue to make inroads into understanding the complex neurobiological underpinnings of cocaine dependence and to identify promising new agents for study in clinical trials. The future of treatment for this widely prevalent and disabling disorder presents difficult challenges, but there are many possibilities for solutions that await further investigation.

**TABLE 10.** *Future directions.*

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**Cocaine agonists in preclinical studies**

Rationale: Drugs with mild psychomotor stimulant effects (e.g., DA uptake inhibitors), but with other effects that may block the positive effects of cocaine or enhance the negative effects of cocaine.

- (Acri et al. 1994)
  **GBR12935:** Potent and highly selective DA uptake inhibitor.
  **Benztropine:** DA uptake inhibitor with muscarinic antagonist activity.
  **Ifenprodil:** Inhibits DA uptake at concentrations comparable to those observed for cocaine.
  **GBR12935:** Increased locomotor activity in mice; substituted for cocaine in rats trained to discriminate cocaine; enhanced cocaine effects; caused convulsions alone and in combination with cocaine.

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**TABLE 10.** *Future directions (continued).*

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**Ifenprodil:** Attenuated stimulant effects of cocaine at doses that did not reduce spontaneous activity when given alone.

**Benztropine:** Increased locomotor activity in mice and substituted for cocaine in rats trained to discriminate cocaine; overall low efficacy as a stimulant, reduced ability to enhance behavioral effects of cocaine, no evidence of toxicity alone or with cocaine.

- (Glowa et al. 1994)
  **GBR 12909:** Decreased cocaine responding in monkeys and was not self-administered by cocaine naive monkeys.

**Cocaine antagonists in preliminary studies**

Rationale: Blockade of cocaine pharmacological effects by treatment with drugs with specific targets may alter acute cocaine effects.

- (Kosten and Nestler 1994)
  **Clozapine:** An atypical neuroleptic has been shown to inhibit cocaine-conditioned place preference.

- (Heidbreder and Shippenberg 1994)
  **SCH23390:** A $D_1$ antagonist that has been shown to attenuate cocaine effects in an animal model.

- (Sepinwall et al. 1992)
  **Dextrophan and dextromethorphan:** NMDA antagonists that have shown some evidence for attenuation of cocaine effects in animal studies.

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# Methodologic Recommendations for Cocaine Abuse Clinical Trials: A Clinician-Researcher's Perspective

*Edward V. Nunes*

## INTRODUCTION

Dozens of medications have been tested as treatments for cocaine abuse, but none has shown clear promise (Kosten 1992; O'Brien 1993). Intensive psychosocial treatments have shown some efficacy (Carroll et al. 1991; Higgins et al. 1991, 1993; Magura et al. 1994; McLellan et al. 1993; O'Brien 1993; Rawson et al. 1990, 1991), but even with these, dropout rates and failure rates remain significant, and powerful medication treatments for cocaine abuse are still needed.

This chapter develops the thesis that the medications development effort for cocaine abuse would be improved by focusing on two problems:

1. Viewing cocaine abuse as a unitary syndrome and testing drugs on unselected samples. Instead, cocaine abusers may be heterogenous and divisible into subgroups, which may respond to different treatment approaches. For example, depression, attention-deficit hyperactivity disorder, and alcohol abuse or dependence all co-occur frequently with cocaine abuse and are all amenable to pharmacotherapy.

2. Reliance upon simple open-label pilot trials in choosing promising medications for further testing. Open-pilot trials have tended to create false impressions of efficacy, which have not been borne out in large placebo-controlled trials. O'Brien (1993) has challenged the field to come up with alternatives to the open-pilot trial. Designs for small, controlled pilot trials will be discussed.

This chapter builds from a review of controlled trials of tricyclic antidepressants, mainly desipramine, for treatment of cocaine abuse. This is the most thoroughly studied medication to date for treating cocaine abuse and will serve as a case example, highlighting the difficulties in testing medications for cocaine and motivating subsequent methodologic recommendations.

## CONTROLLED TRIALS OF TRICYCLIC ANTIDEPRESSANTS FOR COCAINE ABUSE

Prospective, parallel group, placebo-controlled trials were selected for review. In the following narrative, each trial is summarized, while the main outcomes are collated in table 1.

The ground-breaking placebo-controlled trial of desipramine was that by Gawin and colleagues (1989). Twenty-four patients completed at least 1 week of treatment in each of three groups: placebo, desipramine, and lithium were compared. Fifty percent of the sample were intranasal (IN) users. The patients received counseling once per week in addition to medication. Patients who dropped out during the first week after randomization were replaced. The overall dropout rate at 6 weeks of treatment, including those early dropouts, was about 45 percent. Desipramine patients remained in treatment significantly longer than the other groups. The proportion of patients with 3 or more consecutive cocaine-free weeks, urine confirmed, was significantly greater on desipramine (59 percent) than placebo (17 percent). Robust effects of desipramine, compared to placebo, were also found for quantity of cocaine use and for cocaine craving, both self-report measures. For all groups, there was a substantial reduction in both cocaine use and craving during the first week of treatment, suggesting a moderate-sized placebo effect on these self-report measures. Outcome of mood or psychological symptoms was not reported, and less than 20 percent of the sample had comorbid DSM-III mood or anxiety disorders. However, removal of the small subgroup with depressive disorders did not alter the favorable desipramine effects. In summary, this trial replicated previous open-label trials in suggesting substantial efficacy for desipramine in unselected cocaine abusers.

A small, early trial by Giannini and Billett (1987) is of interest because mood, instead of cocaine use, was the main outcome measure, and again desipramine was found superior to placebo. Neither cocaine use nor craving was measured in this trial. The trial is also muddied because the desipramine group also received bromocriptine, which was discontinued after the early weeks of treatment with patients remaining on desipramine.

**TABLE 1.** *Summary of controlled trials of tricyclic antidepressants for cocaine abuse.*

| | Percent Intranasal Users | Dropout Rate | Abstinence Measures DMI > PBO | Self-Report Cocaine Use DMI > PBO | Cocaine Craving DMI > PBO | Depression/ Psych Sxs DMI > PBO | Subgroups with Greater Medication Effect |
|---|---|---|---|---|---|---|---|
| Gawin et al. (1989) | 50 | 45% @ 6 weeks | + | + (p) | + (p) | | (removal of small depressed subgroup did not change effects) |
| Giannini et al. (1987) | | | | | | + | |
| Weddington et al. (1991) | 30 | 50% @ 4 weeks | + (trend) | - (pp) | - (pp) | - (pp) | |
| Kosten et al. (1992) | 11 | 25% @ 12 weeks | - | - (p) | - (p) | + | Patients with depression or without antisocial personality |
| Arndt et al. (1992) | (majority using IV) | 20% @ 12 weeks | - | + (weeks 2, 4)<br>- (weeks 8, 12) | - | | Patients without antisocial personality |
| Carroll et al. (1994) | 29 | 21% @ 2 weeks<br>65% @ 12 weeks | - pp | - (p) | - (p) | - (p) | Patients with milder cocaine abuse |
| Nunes et al. (1995) | 46 | 46% @ 4 weeks | + (trend) | - (p) | + (p) | + | Patients with depression or intranasal use |

KEY: (p) = moderate placebo response; (pp) = large placebo response.

Weddington and colleagues (1991) compared cocaine abusers who completed at least 2 weeks of treatment on desipramine (N = 17), placebo (N = 21), and amantadine (N = 16) over a 12-week trial. The sample consisted of only 30 percent IN cocaine users. In addition to medication, patients received twice-weekly psychotherapy. The dropout rate was about 50 percent by week 4, if those who dropped out prior to week 2 are included. The number of weeks of consecutive, urine-confirmed cocaine-free weeks was analyzed as a continuous measure. The report shows a one-way ANOVA comparing the three groups, which was not significant. However, a test of the difference between the desipramine and placebo means would be a more appropriate gauge of the desipramine effect. Comparing the means (± standard error of mean) reported for the desipramine (6.2±1.1) and placebo (3.6±0.8) groups yields a $t$-statistic of 1.96 with 36 degrees of freedom, which is a trend ($p < 0.10$) for a two-tailed test. An argument could even be made for a one-tailed test (which would be significant here at the 0.05 level), since consecutive cocaine-free weeks was a primary outcome measure in the previous trial (Gawin et al. 1989), and this trial was a replication attempt. For self-report cocaine use and craving, there were even greater reductions across groups during the first week than those observed by Gawin and colleagues (1989), again suggestive of a substantial early placebo effect. With such large placebo effects, demonstration of medication-placebo differences would be very difficult, and in fact none were observed on these measures. Mood outcome in the form of weekly Beck Depression Inventory scores was reported in this trial. There was no desipramine-placebo difference on the Beck, although the mean baseline score was less than 10, suggesting the sample was at most mildly depressed to begin with, leaving little room to demonstrate improvement from an antidepressant. This trial has generally been presented as a negative study and a failure to replicate. However, substantial placebo effects on most measures, as well as relatively small sample sizes, severely limit statistical power. Interestingly, on consecutive cocaine-free weeks there is a less pronounced placebo effect and a marginally significant desipramine-placebo difference.

A pair of studies were subsequently published evaluating desipramine for cocaine abuse in methadone maintenance patients. Arndt and colleagues (1992) randomized 79 patients to desipramine or placebo: 83 percent were intravenous (IV) users and only 11 percent were IN users. The dropout rate was only 25 percent at 12 weeks, substantially less than in the previous studies, likely reflecting the power of methadone in a well-run, multimodality clinic. Side effects and the dropout rate were greater on desipramine than placebo. No desipramine-placebo differences were detected on self-reported cocaine use or cocaine craving, and scores for these were about 40 percent reduced between baseline and end-study in the placebo group, suggesting modest placebo effects. In contrast, the proportion of drug-positive urines remained high throughout the trial, ranging from 60 percent to 90 percent, with no significant desipramine-placebo difference, and little trend toward reduction in the placebo group over time. Thus, similar to the pattern noted for other studies, abstinence rates were relatively low with little placebo effect. A number of Addiction Severity Index (ASI) factor scores and measures were analyzed, and none showed significant desipramine-placebo differences except for measures of psychiatric problems, where desipramine demonstrated a significant beneficial effect. A secondary analysis has subsequently suggested that medication effects were greater when patients with antisocial personality are removed (Arndt et al. 1994).

Kosten and colleagues (1992*b*) randomized 94 methadone maintenance patients abusing cocaine to desipramine (N = 30), amantadine (N = 33), or placebo (N = 31) for a 12-week trial. The majority of patients were IV users. Dropout rates were again relatively low at 27 percent on desipramine and 13 percent on placebo. Interpretation of outcome is hampered by the fact that desipramine and amantadine effects are not separated. For self-report cocaine use there was a significant advantage for medication over placebo in the second and fourth weeks of the trial, but no differences later in the trial. Again, abstinence rates were low, with little improvement over time (i.e., little placebo effect), and no medication-placebo differences. In contrast to the other trials, there was also little improvement in self-report cocaine use or craving over time. A secondary analysis (Ziedonis and Kosten 1991) suggested the subgroup with depression may have done better on medication than on placebo. Another secondary analysis suggested medication effects were enhanced by removing the subgroup with antisocial personality (Leal et al. 1994).

Carroll and colleagues (1994*a*, 1994*b*) randomized outpatient cocaine abusers (not on methadone) to two levels of psychotherapy (relapse prevention or case management) and two levels of medication (desipramine or placebo). There were 139 patients randomized; 110 completed two or more treatment sessions and 49 completed all 12 weeks, a large dropout rate consistent with that observed in the other outpatient studies. The majority (62 percent) were freebase users, while

29 percent were IN users. There were no effects of medication assignment on any major outcome measures. Self-report measures of cocaine abuse and for psychological problems (ASI composite scores) showed moderate reductions over time on placebo. In a departure from other trials, the proportion of abstinent days was high, around 70 percent in all groups. Analysis of interactions suggested a significant advantage for desipramine over placebo on consecutive-abstinent days in the subgroup with low-severity cocaine abuse at baseline.

The author and colleagues (Nunes et al., submitted) randomized 113 outpatient cocaine abusers to imipramine or placebo. All patients received once-per-week counseling. Slightly under half the sample (46 percent) were IN users. The attrition rate at 4 weeks was 46 percent (52/113). There were no medication-placebo differences in self-report cocaine use. Interestingly, for abstinence-based measures, there were at least trends favoring imipramine. Among 4-week completers, the proportion of patients with three consecutive cocaine-free weeks, urine-confirmed, was 11/34 (32 percent) on imipramine versus 3/27 (11 percent) on placebo ($p < 0.10$). There were again moderate-sized reductions in self-report cocaine use and craving on placebo over time. Imipramine was superior to placebo on craving and on the Hamilton Rating Scale for Depression score. This study differed from the others in that it was stratified prospectively by route of cocaine use and by level of depression. Analysis of these subgroups suggested the imipramine effect on abstinence was occurring mainly among the IN and depressed patients.

## Summary of the Controlled Tricyclic Trials

Considering these trials together, and inspecting table 1, several points become clear.

1. Dropout rates: Dropout rates are high, especially in the early weeks of treatment.

2. Placebo effects: Substantial placebo effects are evident for self-report measures of drug use and craving, although not for measures of urine-confirmed abstinence.

3. Efficacy: The overall impression of efficacy, based both on review of these trials and the author's experience treating patients in his own trial, suggests there is something there—some effect on craving, or mood, or on cocaine use early in the trial, or perhaps in some

subgroup of patients. However, the effect is modest and certainly not a large effect such as that of methadone upon opiate dependence.

4. Subgroup hypotheses: Inspection of table 1 suggests tricyclic effects on cocaine use may increase with the proportion of IN users in the sample, suggesting that the subgroup of nasal users may be more responsive. Posthoc analyses of several trials have suggested other subgroup hypotheses—that depressed cocaine users (Ziedonis and Kosten 1991) and mild cocaine users (Carroll et al. 1994*a*, 1994*b*) may respond preferentially, and that cocaine users with antisocial personality do not respond (Arndt et al. 1994; Leal et al. 1994). In the author's trial, IN and depressed groups, identified prospectively, appeared to respond preferentially.

## METHODOLOGIC ISSUES AND RECOMMENDATIONS

### Sample Heterogeneity and Targeting Subgroups

Klein (1991) has argued that failure to recognize sample heterogeneity can easily doom a drug development effort. If response is restricted to a subgroup, and this is not recognized early in Phase II, subsequent large Phase II or Phase III trials may falter because study samples are diluted with unresponsive patients. As noted in this chapter, subgroups based on addiction severity, route of use, or depression may be relevant to cocaine abuse pharmacotherapy and should be considered when devising interventions and designing clinical trials, either in terms of restriction of inclusion criteria or stratification.

A relatively unexplored strategy is treatment of comorbid psychopathology among cocaine abusers. Comorbid psychopathology is more prevalent among substance abusers than in the general population (Regier et al. 1990) and has consistently been associated with poor prognosis (Carroll et al. 1993; Kosten et al. 1986; Rounsaville et al. 1982, 1986). To the extent that psychopathology may contribute to the etiology of substance abuse in an individual, treatment of the psychopathology should improve outcome.

Treatment of depression with tricyclics in alcoholics and opiate addicts has received some study. The author (Nunes and Quitkin, in press) has recently reviewed this literature. The consensus from these is encouraging in that depression appears identifiable and treatable. Such treatment may improve substance abuse, although the evidence for this is weaker. It seems likely that this strategy will prove to be a useful adjunct to substance abuse treatment, but will not yield a large-sized effect akin to methadone for opiate dependence. Nevertheless, in the absence of powerful and globally effective anticocaine agents, such subgroup strategies are probably worth pursuing.

Further, among cocaine abusers, there has been little study of the treatment of subgroups with comorbid psychopathology. In addition to depression, alcoholism, antisocial personality, attention-deficit disorder, and schizophrenia are all associated with cocaine abuse. All but antisocial personality can be effectively treated with pharmacotherapy. Thus, a series of studies suggest themselves to determine the extent to which targeting comorbid psychopathology is useful in cocaine abuse.

## The Placebo Effect and Open-Pilot Trials for Cocaine Abuse

Reflection on the placebo groups in the controlled tricyclic trials suggests why open-pilot trials are likely to yield false-positive results and reinforces the notion (Kosten 1992; O'Brien 1993) that this design may be fundamentally flawed as a medications development tool for cocaine abuse. In most of the trials, clear reductions over time in self-report quantity of cocaine use and "craving" were observed, especially over the first 1 to 3 weeks of the trial. Were these uncontrolled pilot trials of new agents, most would have been interpreted as indicating efficacy.

These "placebo" effects are probably created, in part, by the psychosocial interventions that accompanied pharmacotherapy. All the trials provided at least once-weekly counseling visits, and some provided more (Carroll et al. 1994*a*, 1994*b*; Weddington et al. 1991). Another contributor may be a reporting bias in which patients, perhaps wishing to please their clinicians or significant others, report less cocaine use over time when there had in fact been little real change. This would be consistent with the observation that placebo effects were more prominent for self-report measures, whereas for more objective measures, urine-confirmed abstinence, and retention, there was less placebo effect and dropout, and nonabstinence rates remained high. A tendency of sicker patients to drop out, leaving the sample progressively enriched with less severe cases, could also help create the impression of improvement over time.

Placebo effects varied in strength across trials. This may simply represent fluctuations due to sampling or differences between local populations. However, it may also be that the psychosocial interventions differed in their efficacy. This promoted the argument that an overly effective psychosocial intervention might overwhelm medication effects and that medications should therefore be tested in the setting of minimal psychosocial interventions. On the contrary, the relatively high rates of dropout and of failure to achieve abstinence suggest there would still be plenty of room for a medication to demonstrate an effect in such trials. An argument can be made that medication trials should be superimposed on a strong psychosocial intervention, so that the trial is informative in terms of what medication has to add to good standard treatment. Anything less may lack clinical credibility with the control group becoming a "straw man" receiving poor care. The field can look to the experience with methadone, which shows that this highly efficacious medication is best applied in an adequate psychotherapeutic setting (McLellan et al. 1993).

## Recommendations

The above features of "placebo response" in cocaine abusers suggest the following design features for preliminary trials:

1. A single-blind placebo lead-in phase: A 2-week, single-blind placebo lead-in would "wash out" the early placebo effect and early dropouts and provide a more stable baseline. The one disadvantage of this feature would be loss of the opportunity to see a medication effect on early attrition. On the other hand, much early attrition may relate to insufficient motivation and occur before a minimum adequate exposure to medication has occurred.

   The utility of the initial placebo lead-in phase has recently been challenged in the setting of medication trials for outpatient depression, based on analyses showing that it reduces ultimate response rates about equally across groups and therefore does not sharpen the discrimination between placebo and medication (Trivedi and Rush 1994). On the other hand, Quitkin and colleagues have shown, again in the setting of depression trials, that removal of early responses (Quitkin et al. 1993) or covariation by degree of early response (Quitkin et al., submitted), does enhance power, although the advantage may be slight (Quitkin et al., submitted). In cocaine abuse trials the advantage is likely to be greater, since early placebo effects, and early attrition, are more pronounced.

2. Some form of concurrent placebo control: Given the evident variation in placebo effects in cocaine abuse trials, some estimate of the placebo effect within the sample of a pilot study is needed, even if the sample size is small.

3. A standardized and potent psychosocial intervention: The goals of this would be to reduce attrition and reduce variation contributed by nonpharmacologic factors. This would best be manual driven, so that all patients receive approximately the same "dose" of psychosocial/behavioral therapy. For example, relapse prevention (Carroll et al. 1991, 1994*b*) has demonstrated efficacy and is a reasonable choice. Simple once-per-week counseling is probably not adequate treatment for outpatient cocaine abusers (Kang et al. 1991), and trials may need to provide more than this, particularly in the early weeks.

Providing positive incentives, contingent on clean urines, has proved a powerful intervention (Higgins et al. 1991, 1993), and this might indeed overpower medication effects. However, not all patients respond. Medication might be tested as an adjunct in the incentive-refractory group, and this could be viewed as another example of the strategy of restricting the inclusion criteria to target a specific subgroup and reduce sample heterogeneity. Incentives might also be applied, contingent on attendance, to improve retention in medication trials.

## Measurement of Outcome in Cocaine Abuse Pilot Trials

A second set of problems reflected in the controlled tricyclic trials has to do with measurement of outcome. Reduced quantity of cocaine use by self-report may not be all that meaningful clinically. Patients wishing to please clinician-investigators may report less use over time, giving the appearance of improvement in within-subjects comparisons (i.e., an expectancy effect). The same problems may apply to retrospective self-reports of craving. Objective outcomes may be more likely meaningful. Urines remain the "gold standard" for documenting abstinence, ultimately the most desirable outcome. Quantitative urine cocaine metabolites from at least two samples per week may provide more objective documentation of reduced use short of abstinence (Batki et al. 1993). Several chapters in this monograph present promising new methods for analyzing quantitative urines (Preston et al., this volume).

Response to cocaine-related cues in the laboratory also deserves consideration. Cue response has been associated with relapse (Ehrman et al. 1993) and includes objective physiologic measures (Childress et al. 1992; Ehrman et al. 1992).

Nevertheless, Klein (1991) argues that in preliminary Phase II trials, experienced clinicians should follow the patients because they may observe important improvements not detected by the planned primary outcome measures, or conversely they may judge improvement in some primary outcome measure to be of little clinical significance. The author found that direct clinical involvement with patients in his own trial was helpful in interpreting the numerical outcomes.

Quitkin and colleagues (1984) and Klein (1991) also argue for the importance of observing patients on a medication beyond an initial 6-week acute trial in a "maintained improver" design. An effect slow to develop could be missed in a 6-week trial. More importantly, acute improvements will be more clinically meaningful if sustained over time, whereas transient improvements and "placebo effects" will wash out. For example, in Gawin and colleagues' (1989) original 6-week desipramine trial, the response criterion of three or more consecutive, urine-confirmed, cocaine-free weeks would be more impressive if supplemented by a second 6 weeks of observation on medication as opposed to long-term naturalistic followup during which treatment is no longer controlled by design (Kosten 1992*b*).

Quitkin and Rabkin (1981) and Klein (1991) argue that it is useful to study the medication withdrawal process systematically. For patients who have improved on a medication, tapering back to placebo can increase the information yield, since true medication responders should relapse on placebo. This placebo-controlled discontinuation design is discussed further below.

## Recommendations for Design and Measurement

1. Emphasize "objective" outcome measures, including urine-confirmed abstinence, quantitative urine-cocaine metabolites, and possibly response to cocaine-related cues.

2. Retain a role for the experienced clinician in judging whether a clinically significant improvement has occurred and identifying responsive subgroups.

3. Consider the "maintained improver" design (Quitkin et al. 1984), in which patients remain on medication for a total of 12 weeks, a 6-week acute trial followed by a 6-week maintenance phase.

4. Consider the placebo-controlled discontinuation design (Quitkin and Rabkin 1981), in which patients are systematically tapered from medication back to placebo.

## POTENTIAL EARLY PHASE II DESIGNS

Drawing together the methodologic issues discussed earlier, several designs are considered as likely improvements over the open-pilot trial. Again, the goal for "early Phase II" is to test drugs for preliminary indications of safety and efficacy in small samples before moving on to larger, more costly controlled trials. Each of the following designs incorporates some form of placebo control and has features that enhance power, allowing smaller samples to be utilized. In keeping with the recommendations mentioned previously, all these designs can include an initial placebo washout phase and a manualized psychosocial intervention, received by all subjects, to enhance retention and teach skills of abstinence initiation and relapse prevention.

### The Two-Period Crossover Design

This is a classic design aimed at extracting the maximum information from a small sample. Power is in theory enhanced by the fact that each patient serves as his or her own control. This design is best for detecting effects with rapid onset, rapid offset, and few withdrawal or "carryover" effects, in samples with low dropout rates (Fleiss 1986). Unfortunately, it is not clear what offset or "carryover" effects might occur with a cocaine abuse medication, and further, despite best efforts at providing a psychotherapeutic foundation, dropouts will occur. Batki and colleagues (1994) employed this design to test fenfluramine in cocaine-abusing methadone patients. Interpretation of the results was clouded both by dropouts and also by an effect of time, such that patients in both groups who were retained into the second period had reduced cocaine use compared to the first period. Both the dropout and time effects are consistent with the results of the desipramine trials reviewed earlier and are likely to hamper efforts to employ this design. However, it might still be considered in stable samples under highly controlled conditions such as inpatient or intensive residential or day-treatment settings.

## The Placebo-Controlled Discontinuation Trial

In this design, patients are at first treated in an open-label trial, and responders are then randomly assigned to either remain on medication or taper to placebo under a double-blind. This has the advantage of an open-label trial that a larger number of patients get initial exposure to the candidate medication. The open-label phase can be analyzed for predictors of response. Only the relatively homogenous sample of treatment responders enters the placebo-controlled phase, reducing heterogeneity and in theory enhancing power (Klein 1991; Quitkin and Rabkin 1981). This would seem a particular advantage, given the suggestions from the tricyclic trials that subgroups (antisocial personality, mild severity, route of use, depression) may be relevant to response. Of course, the randomized experiment in this design bears more on maintenance of response or relapse prevention, whereas a prospective randomized trial bears on induction of initial response. These are different questions, both relevant to cocaine abuse medications development.

The author and colleagues have successfully applied this design to a study of imipramine treatment for depressed alcoholics (Nunes et al. 1993). However, a large number of patients had to be entered initially (N = 85) in order to randomize a small number (N = 26), so that the effort was ultimately larger and more labor intensive than one might like for an initial pilot trial. This is partly due to dropouts and nonresponders in the open phase, and partly to the problem that patients who are doing well on open-label medication are often reluctant to be randomized with a risk of coming off medication.

## The Multiple Baselines Design

In a simple form of this design, patients are randomly assigned to two groups, one of which receives the candidate medication and the other placebo. At a later timepoint, the placebo group is crossed over to medication. This provides an initial prospective, parallel-group, placebo-controlled trial, yielding an estimate of the placebo effect against which the effect of the candidate can be judged. At the same time, this design affords advantage of the open-label trial that most patients (i.e., those who do not drop out) can be observed on medication. Such designs have yet to be implemented in clinical trials of medications for substance abuse.

## A Proposed Hybrid Design

Table 2 describes a hybrid design that combines features of the multiple-baseline, crossover, and discontinuation designs. Treatment-seeking cocaine abusers enter a 2-week, single-blind, placebo baseline phase, after which they are randomly assigned to one of two groups as summarized in table 2, below.

**TABLE 2.** *Proposed design for pilot clinical trials for cocaine medications.*

| | Schedule | | | | |
|---|---|---|---|---|---|
| | 2-Week Baseline | Weeks 1-6 | Weeks 7-12 | Weeks 13-18 | Weeks 19-24 |
| Group 1 | Placebo | Candidate | Candidate | Placebo | Placebo |
| Group 2 | Placebo | Placebo | Candidate | Candidate | Placebo |

The extended single-blind placebo phase at the front end is designed to wash out early dropouts and early placebo effects. The first two 6-week phases (weeks 1 through 6 and weeks 7 through 12) form a multiple-baselines design, as discussed earlier. Finally, patients remaining in treatment during weeks 13 through 24 are systematically tapered back to placebo (double-blind), affording the opportunity to observe whether symptoms of cocaine abuse recrudesce off medication, as in a crossover or discontinuation design. For subjects who complete the entire trial, the design may be viewed as an ABA design, or a series of single-subject experiments. Ultimately, the results of the initial between-groups comparison (weeks 1 through 6) would be synthesized with the crossover discontinuations and within-subjects comparisons, over several outcomes, and with clinicians' impressions, to arrive at a preliminary impression of efficacy, safety, and tolerability.

## Data Analysis, Sample Size, and Power Considerations

Early Phase II clinical trials, such as the designs described previously, are preliminary, exploratory studies with the purpose of suggesting whether a candidate medication warrants consideration for larger, more definitive trials. As such, investigators should be more concerned about missing a true effect (Type II error) and more tolerant of a Type I error, than in a larger, more definitive study.

The author would also argue that investigators should be interested mainly in detecting medium to large effects. While small effects might be of some theoretical interest, they are unlikely to have much clinical impact on cocaine abuse.

Power will be discussed mainly with respect to a between-groups medication versus placebo comparison, such as at the 6-week endpoint in the hybrid design presented earlier. Power of within-subjects comparisons (baseline versus endpoint on medication or ABA designs) or of crossovers may be greater, although potentially more clouded, by effects of time in treatment and attrition.

On an abstinence-based, dichotomous response measure, a low placebo response rate could be anticipated based on the desipramine-placebo trials reviewed earlier. Assuming a placebo response rate of 10 percent, a sample size of 30 patients (15 per group) is sufficient to detect large effects (10 percent response on placebo versus 65 percent on medication), given the usual assumptions of beta = 0.20 and two-tailed alpha = 0.05. Relaxing alpha to = 0.20 will begin to permit detection of medium-sized effects (10 percent response versus 50 percent), at the expense of a greater Type I error rate (Fleiss 1981). Likewise, for continuous measures such as self-report cocaine use, proportion of positive urines across the weeks of a trial, or quantitative urine cocaine metabolites, setting beta at 0.20 and two-tailed alpha ranging from 0.05 to 0.20, 15 per group is sufficient to detect large (1.1) to medium-large (0.80) effect sizes (Cohen and Cohen 1983). These power estimates are based on simple two-group comparisons. Power may be enhanced by stratifying the randomization on baseline severity of cocaine use, and by entering baseline levels of outcome measures as covariates in the data analysis. To the extent that baseline correlates with outcome, power is increased (Fleiss 1986; Klein and Ross 1993). The single-blind placebo lead-in, by reducing variance contributed by early placebo effects, should protect power.

These power calculations assume two-tailed alphas. It can be argued that interest is only in the one-tailed hypothesis that medication is superior to placebo. Again, the goal is to determine whether a positive effect is likely and whether further investigation with the candidate medication is warranted. Failure to find an effect and finding medication worse than placebo would have similar implications, namely to discourage further research with that agent.

At N = 30, the designs proposed herein would not be highly powered to detect statistical significance, particularly for small- to medium-sized effects. However, Cohen and Cohen (1983) argued that clinical investigators should be more concerned with the sizes of effects than with statistical significance per se. A useful alternative approach, then, for early Phase II trials would be to place confidence limits on the effect size. Investigators can then judge whether the likely range of effect sizes warrants further trials. For example, it can be shown that with a sample size of 15 per group, an observed effect size less than or equal to zero virtually rules out a true effect in the medium to large range. The more the observed effect exceeds zero, the greater the probability of a medium to large effect.

## IMPORTANCE OF LABORATORY MODELS

Medications development for many mental disorders enjoys the advantage of prototype-effective medications. Examples include methadone for opiate dependence or various medications effective against depression. These prototypes can be used to validate laboratory models, which then serve to screen and identify new agents with potential efficacy. The prototype can also guide initial clinical observations, serving as a model for how an effective agent should perform clinically and what outcome measures are most appropriate. An overarching problem with medications development for cocaine abuse is that no such anticocaine prototype exists (O'Brien 1993). Nevertheless, animal and human laboratory models with face validity and at least limited predictive validity exist, and clinical investigations need to be informed by them. Animal models will serve as a source of hypotheses for candidate medications. Cocaine choice (Fischman et al. 1990) and cue response (Childress et al. 1992; Ehrman et al. 1992) procedures are human laboratory models that can be used to test potential medications. Early Phase II trials might be enhanced by coordinated efforts between clinical trials and human laboratory studies. Testing the same medication in both the clinic and the laboratory would broaden the available data on safety and efficacy and perhaps provide a clearer recommendation as to whether a medication is promising for further Phase II or Phase III testing.

## THE ROLE OF THE CLINICIAN-INVESTIGATOR

As discussed previously, Klein (1991) emphasizes the involvement of clinician-investigators during early Phase II, arguing that their depth of clinical experience can help to judge clinical significance when statistical significance is detected on some measures, or to perceive responsive or unresponsive subgroups. Direct work with patients can also yield hypotheses, and the history of psychopharmacology includes many advances that began with serendipity and clinical observation.

Not surprisingly, then, many of the most senior principal investigators and center directors at the National Institute on Drug Abuse (NIDA) have strong clinical roots. At the author's own institution, the role of research-psychiatrist has always involved substantial clinical work. However, the balance of priorities needed to flourish in the traditional research-physician or research-clinician role is becoming more difficult to achieve. Increased sophistication and complexity of methodologies, regulatory burdens, and funding requirements, among other issues, will perforce tend to draw principal investigators away from regular contact with patients. A clinician-investigator who spends substantial time with patients runs the risk of producing too few papers, grants, and new initiatives to keep a research operation going. Some balance needs to be struck. Furthermore, a steady supply of new clinician-investigators is needed. NIDA is, therefore, to be encouraged in its commitment to the funding of fellowships and other early career mechanisms that afford research training to clinicians and clinical experience to researchers.

## SUMMARY AND CONCLUSIONS

This chapter reviewed the controlled tricyclic trials for cocaine abuse with both a clinician's and a researcher's eye in order to develop methodologic recommendations for future medications development efforts. The review is summarized in table 2. The main points are that attrition is high, particularly early in the trials; placebo effects are high, particularly early and in subjective or self-report measures; and the samples may be heterogeneous with responsive (depressed, mild severity) and unresponsive (antisocial personality) subgroups.

Methodologic recommendations are summarized in table 3. Emphasis is placed upon the potential heterogeneity of cocaine abusers and targeting

**TABLE 3.** *Summary of methodologic recommendations for early Phase II clinical trials of medications for cocaine abuse.*

| Methodologic Problem | Proposed Solutions |
|---|---|
| Sample heterogeneity | • Target subgroups (based, for example, on comorbid psychopathology, route, or severity) either by restricting inclusion or stratification. |
| Large placebo effects (especially on self-report and subjective measures) | • Emphasize objective measures (e.g., urine-confirmed abstinence).<br>• Single-blind placebo lead-in to wash out early placebo effects and provide more stable baseline.<br>• Discard the uncontrolled, open-label pilot trial in favor of small controlled pilot trials with concurrent randomized placebo control.<br>• Standardized psychosocial intervention. |
| High attrition | • Single-blind placebo lead-in to wash out early dropouts.<br>• Increase intensity of psychosocial intervention. |
| Measurement issues | • Emphasize objective measures, mainly urine-based measures; consider also cue response.<br>• Weigh the observations of experienced clinicians. |

treatments to subgroups on the one hand, and various methodologic recommendations to tighten up the design of early, small-scale pilot trials on the other. These include use of potent, standardized interventions to reduce attrition; a prolonged, single-blind placebo lead-in to wash out early dropouts and placebo effects; discarding the uncontrolled pilot trial in favor of crossover, discontinuation, or multiple-baselines designs; and considering the impressions of experienced clinicians as well as objective, urine-based measures when judging efficacy. These recommendations are all arguable in that they have disadvantages as well as advantages and that they all depart to some extent from current practice and wisdom. It is hoped that they will promote discussion and stimulate methodologic innovation in the search for effective medications for cocaine abuse.

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# Management of Clinical Trials With New Medications for Cocaine Dependence and Abuse

*Ari Kiev*

## INTRODUCTION

Clinical trials of medicines for cocaine dependence are extremely complex to conduct because of the varied nature of cocaine abusers, imprecise methods of diagnosis, lack of well-defined endpoints that can be measured independently of the subjective judgment of the clinician and subject, lack of standardized rating scales, and lack of interrater reliability. Additional problems in doing such studies pertain to site selection, patient recruitment, patient compliance, and study management.

This chapter examines some of these issues and offers important management guidelines that may prove useful as cocaine abuse trials move toward larger placebo-controlled Phase III studies.

## CLINICAL TRIAL MANAGEMENT ISSUES

Clinical trials represent a significant departure from the ordinary routines of clinical practice, so it is imperative that efforts be made at the outset of a study to address all of the potential problems that may occur in the course of a study.

Essentially, clinical trials require a proactive management approach where the study objectives determine the steps to take to execute the study rather than passively accept results and breakdowns as inherent in the process, or in the patients, or in the condition. It is essential to review every breakdown in the study process from recruitment to maintenance of patients in the study for solutions that may increase participation: Why did the patient drop out? How could that patient have been kept in the study? What are the differences between patients who stay in and who drop out? How many were in previous studies? How are potentially noncompliant patients who drop out shortly after starting recognized? Are there any differences between different screening personnel and enrollment rates and retention rates of different raters? What role did the staff play in the process in terms of attitudes, neglect, failure to follow up, or failure to go the extra mile?

Proactive management means clear-cut responsibilities, clear lines of communication, high levels of accountability, designated personnel, and clear definition of duties for managing the project. It also means a willingness to commit to objectives by doing whatever additional steps it takes to produce the result and not simply attributing poor results to the patient population. This may mean, for example, having someone available in the evening in the early phases of a study who knows inclusion/exclusion criteria so as not to lose eligible patients at the moment when the patient first calls about participating in the study—a telephone call may be the only available window in which to enroll the caller.

It also means focusing on other measures to increase retention, such as telephone calls and home visits between office visits, a regular review of all breakdowns in communication, and introduction of essential procedures to prevent breakdowns such as training staff in the subtleties of study etiquette to bolster patient compliance.

The more complex the inclusion and exclusion criteria, the less well-specified the diagnostic subtypes of patients being studied. This is a special problem because it has not yet been determined how to differentiate different types of patients in terms of type of drug use, frequency of use, route of administration, and the various stages of withdrawal, each of which may require a different treatment strategy and a different model of psychotherapeutic management. Also, it becomes especially difficult to train the staff in terms of the appropriate attitudes and procedures to routinely maintain to ensure participation and compliance with the study protocol.

The deficiencies demonstrated in data audits of clinical trials generally reflect failure in communication among responsible parties and a general breakdown in the process of total quality management.

The most common deficiencies in data audits are the absence of informed consents, inadequate drug accountability, nonadherence to protocol, inadequate and inaccurate recordkeeping, failure to obtain approval from the institutional review board (IRB), and failure to inform the IRB of protocol changes.

Adherence to a higher standard of quality control than what exists in most practice settings requires a clarification of study objectives, commitment to the objectives, and a willingness to keep searching for steps that are missing or procedures and personnel that must be installed whenever problems are encountered. Since it is difficult to anticipate all the possible potential patient presentation problems that must be questioned in light of the inclusion/exclusion criteria, or all the procedural breakdowns that may occur along the way that become protocol violations, it is essential that a mechanism be included for constant monitoring of the process as well as quality control of the case report forms to ensure that as much as possible common problems in data audits, and problems that ensue when applying a theoretical protocol to real-life patients, are recognized early so that corrective measures can be put in place.

It is especially critical to spend time in identifying patterns and sources of problems such as the high rate of dropouts in cocaine abuse drug trials and to determine whether they are due to the unreliability of the patient population or to failures in management. Here it is critical to know more about the different types of cocaine patients and withdrawal patterns so as to ensure that the patients recruited are suitable for the study. It is also important to train the staff in ways of handling the variety of problems that frequently surface in this patient population so that patterns of patient care at the site that may not be entirely suitable for the proper conduct of a study can be identified. It is critical to keep asking what is missing in the staff procedures rather than simply attributing problems of dropouts and no-shows to the underlying condition.

## CLINICAL OBJECTIVES

A number of objectives have been pursued in the search for a medication for cocaine dependence, no doubt because of the different patterns of efficacy and pharmacological and theoretical considerations associated with the different drugs tested (Adams and Durell 1984).

Perhaps the most common objectives sought in most studies have been the cessation or reduction of drug use and drug craving. Other studies have sought to compare the efficacy of a single agent against placebo or against a known drug such as desipramine or bromocriptine, neither of which has achieved the status of a standard as yet.

Additional objectives have included the retention of patients in treatment, as has been demonstrated with desipramine; changes in the patients' occupational, legal, financial, medical, or psychological status (McLellan et al. 1980); a reduction in the use of other drugs of abuse; and a change in risk-taking behavior such as the sharing of needles and unprotected sex with multiple partners (Battjes and Pickens 1988).

Most pharmacological studies for cocaine abuse have focused either on blocking cocaine euphoria with drugs such as imipramine, bromocriptine, trazodone, or neuroleptics like haloperidol, or dealing with withdrawal and craving during the first several weeks of abstinence from cocaine as in studies with desipramine, imipramine, bromocriptine, amantadine, carbamazepine, flupenthixol decanoate, buprenorphine, and fluoxetine (Weddington 1992). While a number of pharmacological agents have shown some promise in leading to a reduction of craving and use among cocaine users, there have been few placebo-controlled trials and no drug has been approved for use in cocaine abuse, nor is there a standard drug against which to run clinical trials.

The best results appear to have been with desipramine, which increased periods of abstinence and decreased cocaine craving in the early phase of outpatient treatment (Gawin and Kleber 1984; Gawin et al. 1989*a*, 1989*b*). In a double-blind randomized trial, 59 percent of patients treated for 6 weeks with desipramine achieved 3 or more weeks of continuous cocaine abstinence compared to 25 percent of those treated with lithium and 17 percent treated with placebo. But desipramine had little effect on reducing attrition and did not decrease relapse to cocaine abuse.

## SITE SELECTION

While much of the recent work in cocaine dependence has been done in university settings or in special settings devoted to the problems of cocaine dependence, larger scale studies will have to expand to other locations as well. It is critical to select sites that are organized for research in a highly regulated environment with dedicated personnel able to pay adequate attention to issues of informed consent, adequate documentation, drug accountability, and recordkeeping.

Site selection is critical to the success of clinical trials. In the prestudy phase it is important to establish that the sites have access to the necessary patients, whether in their own patient pools or from referral sources. Too many studies fall short of their required quotas because of the optimism of clinicians or investigators eager to participate in clinical trials without carefully reviewing whether they have the requisite patient numbers, specifically patients who will meet the inclusion criteria, who will be willing to take a new investigational drug, who will participate in a placebo-controlled study, who will stop taking an existing medicine, who will be subjected to repeated venipunctures, who will make the necessary periodic visits, and so forth.

Patient recruitment, in line with enrollment quotas, is especially important and may be problematic for a given site and investigator. Some clinicians hesitate to enroll patients in placebo-controlled studies. They also may be reluctant to try to overcome the patient's resistance to enroll in a study, equating a proactive approach to enrollment with coercion. Clinicians also may be reluctant to advertise for symptomatic volunteers because of certain long-held beliefs about the unprofessionalism of advertising or the self-selected nature of such patients, even though in many studies this may be the only way to recruit sufficient numbers of appropriate patients.

It is also important at the outset to establish the availability of dedicated staff to ensure adherence to protocol inclusion criteria, to maintain adequate source and regulatory documents, and to keep abreast of the numerous changes and amendments to the protocols that occur during the course of a study. These changes and amendments must be coordinated among the site personnel as well as the sponsor and IRB. In this regard it is critical that onsite staff participate in startup meetings and that a complete meeting of all staff take place at the site at the start of the study to ensure that all logistical details are worked out.

It is important to choreograph patient flow, and to recognize the importance of the right attitude of empathy and interest from the telephone screening person to the lab technician, both of whom are critical for enrolling patients, just as they may unwittingly say the wrong thing to patients and encourage withdrawal. All staff members must be familiar with the focus and philosophy of the project, and scripts should be prepared if necessary so that the limits of what to communicate are known.

Because patient screening is often done by nonclinical personnel, it is important that they be made a central part of the research team and trained in the inclusion/exclusion criteria. Their first contact with the patient establishes a bonding with the site that is necessary to ensure complete participation during the course of the study.

## EXPERIENCED INVESTIGATORS

While independence and self-reliance are highly valued characteristics of physicians in general, the clinical investigator may have to learn certain new skills in teamwork to participate in research in a highly regulated and closely managed framework. While the clinician's medical judgment is ultimately critical, it is crucial to always be assessing activities in the framework of protocol requirements. This means learning to feel comfortable in maintaining close communication with the sponsor or clinical research organization managing a trial, and learning not to hesitate to inquire about uncertain issues so as to avoid making protocol errors.

It is especially important to ensure the availability of the targeted population, as access to depressed and anxious patients and even other difficult-to-locate groups such as schizophrenia and Alzheimer's cases does not necessarily prepare the investigator for the special problems associated with recruiting and maintaining cocaine-dependent patients. The demonstration of past experience, a continuous patient pool, or a proven network of referrals is critical in collecting sites even among experienced investigators. It may be desirable to begin building such a cadre of investigators by initiating smaller studies, in anticipation of the larger scale studies that will be needed in the future.

This will help the investigator build a pool of compliant patients who are not placebo responders and who may be willing to participate in subsequent clinical trials. These small-scale studies may also make it possible to explore different methods of recruitment at particular sites and establish actual numbers of screening calls, the percentage of telephone-screened subjects who keep their appointments, the rate of enrollment of telephone-screened subjects to studies, and the dropout rate. This would help establish a measurable basis for site selection for future large-scale studies.

A significant percentage of cocaine-dependent patients deviate from protocols by dropping out because of cocaine craving, other drug dependencies, and psychiatric illness. Experienced investigators are essential in these studies because of their ability to select compliant patients and to maintain compliance without being overly "psychotherapeutic" and without putting patients at risk. The experienced investigator is also alert to the early warning signs of noncompliance, such as missed first appointments, inconsistencies in the information given on the telephone screen and office screen, ambivalence about signing the informed consent, and a past history of noncompliance or nonresponsiveness to a variety of medication programs. The investigator can make the decision not to include selected patients in a study even though there is pressure to enroll them in terms of a highly demanding timeline. The larger the investigator's network, the easier it is to be selective in including patients to increase full participation and lower the dropout rate.

## PATIENT SELECTION

It is important to identify the best geographic locations and investigative sites where the targeted population can be located. There are geocoded databases that can help with this. Given the high dropout rates in cocaine dependence studies, it is best to locate patients who are working and living with significant others who can facilitate followup.

This is especially true for Phase II and Phase III efficacy studies but less relevant in Phase I studies with less stable chronic users who are needed for safety and interaction studies involving the administration of cocaine. Chronic nontreatment-seeking abusers are suitable for early Phase I studies especially when drug challenges are given or controlled access to the abusable drug is available in a behavioral paradigm to measure directly the effect of the medication on drug-seeking behavior (Fischman et al. 1990). These individuals are not generally included in or suitable for controlled clinical trials of medication because they generally do not want to stop drug use.

In Phase II studies of drugs like flupenthixol, which block the effects of cocaine, crack cocaine users theoretically may use more cocaine to get high and counteract the effects of the medication, as has been demonstrated in lab animals. As such it is usually necessary to include some form of psychotherapy to ensure compliance with such studies, of course possibly adding its own confounding effects.

Ideally the best Phase II studies of safety and efficacy are done with small numbers in controlled inpatient settings for several days to determine tolerance to the medication followed by outpatient treatment. Here the criteria for inclusion are less stringent, and recreational users are often included with chronic users to increase compliance, perhaps at the cost of increasing the variability of the results.

When moving to later Phase II studies and Phase III studies, patient selection becomes more important especially because there are no well-validated rating scales and no standard drug against which to compare new drugs. Without such standardization, trends in decreased cocaine usage at particular sites in multisite studies may sometimes be attributed to the inclusion of nonhomogeneous patient populations or to different treatment approaches at the different sites.

The clinical condition must be defined as precisely as possible. In Phase III trials there is a need to distinguish between recreational and chronic users whose patterns of usage and attitudes toward participation in a study may be significantly different. It is difficult to differentiate between subtypes of patients in terms of type of drug use, frequency of use, route of administration, and the various stages of withdrawal, each of which may require a different treatment strategy and a different model of psychotherapeutic management, making it especially difficult to train staff in terms of the appropriate attitudes and procedures to routinely maintain to ensure participation and compliance with the protocol. It is also important not to define exclusion criteria too rigidly and to leave a large window or grace period for followup visits so that missed visits do not constitute protocol violation.

Local newspaper or radio advertising, which is often essential to recruit the large numbers needed for Phase III trials, may be less useful with the cocaine-using population than is true for symptomatic volunteers with depression and anxiety symptoms. This requires further study. It is also necessary to find new ways of working with traditional sources of referral from other community medical or psychiatric agencies, which oftentimes for philosophical reasons do not support the concept of "testing" new medications in placebo-controlled clinical trials, or are threatened by issues of territoriality. It may be necessary to begin to build relationships with other agencies, including the drug-free therapeutic communities, which seem to have a large number of cocaine-dependent patients in their patient and graduate networks, many of whom may be interested in and may benefit from participation in clinical trials with new medications for cocaine dependence.

Problems at the time of recruitment pertain to problems in diagnosis and making certain only to include those patients who fit the protocol. The same applies to the care with which past medical histories are obtained, so as not to include patients who after starting may reveal the existence of conditions that would exclude them. The initial interview must be extremely thorough and designed in anticipation of subtleties about participation that are not generally considered in the course of routine psychiatric care.

It is important to recruit patients who will be cooperative, compliant, and willing to participate for the duration of the study. Patients must also be capable of following instructions, returning medications, making regular appointments, and adhering to the protocol. Meeting these criteria is especially difficult in the case of cocaine abuse where the condition itself seems to impinge on the very qualities necessary for participation.

The same may be said for certain Axis II personality disorders such as borderline personality and paranoid personality, which may be particularly prevalent among cocaine-abusing patients and which also may contribute to noncompliance in the study.

## HOSPITAL OR OUTPATIENT SETTINGS

There are obvious advantages to hospital settings in terms of the severity of withdrawal patterns, the control over medication and retention, the measurement of side-effect profiles, and the monitoring of plasma levels, all of which are more easily measured because of increased compliance. Hospitals are also better environments in which to conduct challenge studies where patients are given the test medication and then are able to select differing amounts of the drug of abuse in a patient choice paradigm designed to measure the blocking effect of the test medicine.

Chronic users who are most suitable for these studies are easier to find and easier to induce to remain in an inpatient facility than recreational users, but they are often less motivated, have more medical problems, are polysubstance abusers, and when moved to outpatient status may rejoin the ranks of the homeless and be difficult to find for followup visits.

A disadvantage of hospital settings is that they lack the environmental cues and stimuli that often provoke a return to drug abuse and therefore are not realistic settings in which to measure the control of drug dependence with medication. The severity of the patient's illness and the stage of drug testing are critical factors here. To measure cocaine use, craving, and the responsivity to environmental cues, it is preferable to conduct a trial to measure the control of drug dependence with medication in an outpatient department, despite the risk of greater dropouts.

Because patients, especially recreational users, do not want to be confined, there is a need for fast-acting drugs. While these may work, the long-term beneficial effects that may be even more dramatic may be hard to establish because of the problems of following up patients after they have left an inpatient facility.

## COMPLIANCE

Various attempts to increase compliance have been tried. The anecdotal evidence on putting a computer chip in the medicine bottle to see if the patient took the test medicine suggests that these bottles are often opened as much as 25 times a day, making this virtually useless as a measure of compliance. The use of depot flupenthixol to circumvent the issue of compliance has been tried, but it raises ethical questions of inducing in high doses dopamine (DA) side effects such as tardive dyskinesia, which may not be justifiable in this population as it is in patients with psychotic symptomatology. Moreover, some patients may theoretically try to overcome the DA blockade by taking more cocaine and risking overdose. The dropout rate in one such study was 60 percent as compared to a dropout rate of 20 percent on a 6- to 8-week trial of methadone maintenance patients with cocaine abuse. Another way to lower dropout rates is to exclude hardcore patients who are more likely to use other drugs and take more cocaine and to rely more heavily on more motivated individuals who may be living with family members and working, which also may add to compliance. Another approach is to design feasible studies, for example by allowing a wider window for drug administration to accommodate missed visits by patients.

## PSYCHIATRIC DIAGNOSIS

The difficulty of making precise diagnoses often leads to heterogeneous patient samples, which in turn makes it difficult to accurately test the efficacy of new compounds. This is seen in traditional psychiatric trials where there is often difficulty in distinguishing schizophrenia from schizoaffective illness or manic-depressive illness, or in distinguishing discrete episodes of major depression from chronic low-grade depressive mood of dysthymia. The heterogeneity of drug users makes it especially difficult to find treatments that may be effective with a selected portion of the drug-using population that enter into a study. On the other hand, limiting study samples to homogeneous ones may limit the rate of enrollment and generally slow the progress of comparable research at other sites. It is therefore often essential to find some compromise between the two extremes.

In cocaine studies there may be difficulty differentiating chronic users from heavy recreational users. This is especially significant in Phase I safety and interaction studies where it would be acceptable to use chronic users who do not want to stop cocaine, but unethical to use cocaine for nondependent recreational users who are motivated to stop the drug. The distinction between chronic users and heavy recreational users is less significant in Phase II dose-ranging and efficacy studies where the use of recreational users is likely to make it easier to show a response. These patients are usually more compliant and motivated but harder to convince to stay in a facility for the intense tests such as Holter monitoring required for such studies. Differences among patients is also important in Phase III studies attempting to differentiate active drug from placebo and measuring it against a comparator. Fortunately, the problems of diagnosis can be controlled to some extent by the use of standardized criteria and standardized interview schedules, a number of which are available.

## DEFINING THE COCAINE DEPENDENCY SYNDROME

The importance of defining specific diagnostic subgroups to study is underlined by clinical findings of Weddington and his group that cocaine addicts who sought treatment in his research facility reported greatest craving for cocaine during the 24-hour period immediately before admission and the greatest severity of mood distress on day 1 (Weddington et al. 1990). Mood states, craving, and reports of waking during the night and of clearheadedness on awaking improved gradually during the study and were not cyclical or phasic during the first 4 weeks of abstinence. According to Weddington, the absence of cocaine and other drugs as well as drug-taking stimuli in a controlled environment may account for the lack of a classical postabuse abstinence syndrome.

Elsewhere, Meyer and Mirin have proposed that drug craving is an appetitive response: Where drugs are available to addicts, craving is likely (Meyer and Mirin 1979). Wikler demonstrated that craving and physiological responses to drugs and drug-taking cues are affected by classic conditioning of exteroceptive stimuli (Wikler 1973). Other work by Jaffee demonstrated the role of internal stimuli associated with cocaine administration by demonstrating that giving cocaine to experienced cocaine users increases their craving for the drug (Jaffee et al. 1989).

All of this underscores the importance of studying the behavioral and psychological components as well as the physiological components and emphasizes the importance of clearly defining the parameters of the study so as to take these factors into consideration and not simply bunch people all together in heterogeneous samples.

## PATTERNS OF DRUG ABUSE

It is also essential to differentiate among patterns of drug abuse, routes of administration, the frequency of drug use, and the consequences of use in terms of physical dependence, tolerance, craving, drug-induced problems, and neurobiological system dysfunction, such as in the adrenergic, dopaminergic, and serotonergic systems where these drugs act (Blaine et al. 1994).

The stage of drug use is also an important variable. People in the earliest stages of dependence who are more difficult to find are more likely to respond to antagonist medications than those in later stages, and they may be more suitable candidates for testing efficacy than chronic long-term users.

Other factors to consider in differentiating among patients is the nature of prior treatment, prior success in achieving abstinence, time to relapse, or early treatment termination. Additionally, motivation for treatment is a critical variable to assess. Here are encountered the problems of denial and the desire to continue the drug-using pattern.

There may also be difficulty in distinguishing the effects of various anticocaine medications when the patient populations are heterogeneous. A review of some of the recent research literature suggests that diagnostic distinctions must be made between nasal and intravenous users who seem to respond differently in some studies, patients on methadone maintenance as compared to those who are not, and patients suffering from depression and cocaine abuse as in the studies at Yale where depressed cocaine abusers certainly showed some response to desipramine.

Of course it is easier to recommend these finer diagnostic distinctions than it may be to find homogeneous samples of cocaine abusers. The reasons for this are severalfold:

1. Many patients are polysubstance abusers. Even if screening out patients with positive drug screens for opiates or other substances, patients are often unreliable and noncompliant and investigators cannot be certain patients will use only cocaine in the course of the trial. Moreover, the interaction of prescribed opiates such as methadone with cocaine may further compound the results.

2. It is sometimes difficult to differentiate between treatment-resistant chronic users who may be motivated by a need for food and shelter and treatment-seeking chronic users who may qualify or be appropriate for early Phase II studies but not for later studies.

3. Some patients may have multiple psychiatric diagnoses that may not be identified at the screening interview. In addition to cocaine abuse, patients may suffer from major depression or schizophrenia, conditions that may respond to the test drug resulting in some improvement of symptoms and a reduction of the motivation for cocaine without directly impacting on the cocaine abuse itself. This can create obvious problems in the interpretation of the data.

## TREATING PATIENTS WHO ARE CODEPENDENT OR ON OTHER MEDICATION

A number of studies have been conducted with cocaine-dependent individuals who were receiving methadone for opiate abuse. Using such individuals for study can be problematic for several reasons. Multidrug users are less likely to be compliant than single-drug abusers and more problematic to maintain in an outpatient study (Mirin and Weiss 1987). Additionally, the drugs may interact, producing problems in interpreting the data. It has been reported that methadone raises blood levels of desipramine thereby making for complicated dosing of desipramine to control cocaine use and cocaine craving (Kosten et al. 1987). Nevertheless, there is some strong evidence that desipramine and amantadine may be helpful in reducing cocaine use, craving, and depressive symptoms in a group of methadone maintenance patients and that desipramine may be helpful in keeping patients in treatment and cocaine-free at the end of the study (Kolar et al. 1993).

## COMORBIDITY

There is an extremely high incidence of comorbid mental disorders among those with drug use disorders (Regier et al. 1990). In one survey, 76 percent of those with a cocaine abuse or dependence disorder gave a history of mental disorder. Recently Rosen and Kosten found that the incidence of panic attacks among methadone-maintained patients has increased over a 10-year period from 1 to 6 percent to as high as 13 percent as a result of cocaine use as well as environmental and constitutional factors (Rosen and Kosten 1992). Schizophrenic patients have a lifetime prevalence rate of cocaine abuse between 15 percent and 50 percent. In one study of schizophrenic patients in a dual-diagnosis program, patients receiving desipramine and antipsychotic agents were more likely to complete the study and demonstrate substantially decreased cocaine usage than did patients treated with antipsychotic medication alone (Ziedonis et al. 1992).

Other comorbid problems relate to issues of HIV infection, alcohol abuse, and multiple drug abuse patterns. In one study it was found that informing drug abusers in treatment regarding positive HIV serostatus was not associated with a lower treatment retention rate or adverse psychological reactions when counseling regarding HIV issues was integrated with drug abuse treatment (Weddington et al. 1991). Insofar as alcohol and cocaine abuse commonly occur together, it is of interest that treatment for both can be accomplished in the same setting if important demographic and pharmacological differences are addressed (Closser and Kosten 1992). As to multiple drug abuse there have been successful demonstrations of treatment with disulfiram for alcohol-abusing patients and amantadine for cocaine-abusing, methadone-maintained patients (Kosten 1991).

## RATING SCALES

Efficacy of psychiatric medication is often difficult to measure because of the variability of patient responses to medication, especially when the patient sample is heterogeneous. The method of measuring efficacy by having the investigator question the patient and assign symptoms to a rating scale is fraught with error. There is often a high degree of variability in the ways that patients can respond to cue questions and a minimum of interrater reliability regarding diagnosis, which makes for problems in multisite studies. Indeed, there are no validated or universal tools as yet for measuring issues relating to cocaine abuse.

The scales being used in cocaine studies, including the Visual Analog Cocaine Use Scale and the Visual Analog Craving Scale as well as various measures of mood states, are highly subjective and hard to validate without a standard drug against which to compare the test drug. One new test, the Self-Administration Paradigm, where patients get to choose one of two drug regimens after active medication, has some potential for being objective, but it has not been validated as yet.

A review of the literature suggests a wide variety of endpoints being used in studies that make comparisons among studies very difficult. Outcome measures include psychiatric outcomes, craving, subjective drug effects, patterns of drug use, and retention in treatment. The instruments and the data collection methods being used vary from study to study, making comparison of studies virtually impossible. There is an urgent need to standardize or at least reach some consensus on the methodologies, instruments, rating scales, and endpoints used in clinical trials so that cross-trial comparisons can be made, thereby facilitating advancement of knowledge in the field.

There is also the difficulty of differentiating between symptoms and side effects. Patients may be depressed before, during, and after using cocaine. In testing a DA antagonist like flupenthixol, for example, it might be difficult to test whether reports of depression were related to the cocaine use or to the DA depletion caused by the medication. The presence of side effects also may blunt the patient's report of symptomatology. The Hamilton Rating Scale for Depression often used in studies of cocaine dependence is heavily weighted with items relating to insomnia, GI disturbance, and anxiety—all three of which may be adversely affected by selective serotonin uptake inhibitors like fluoxetine, which is being studied at some sites for cocaine dependence. During a trial the scale may indicate an increase in depression when in fact the elevated scores may be due to common physiological side effects of the selective serotonin reuptake inhibitors (SSRIs).

## DURATION OF CLINICAL TRIALS

Many studies have been done that did not last long enough to establish clinical efficacy. Studies must be designed in terms of the pharmacology and the intended use of the medication (Satel and Kosten 1991). The duration of the study needs to be long enough to demonstrate efficacy and yet short enough to ensure retention of enough patients to do the statistical analyses needed to demonstrate treatment effects.

The nature of the condition being studied must be considered so that the study is not so short in duration that it misses certain clinical events associated with the condition such as periodic binging, delayed recovery, or delayed relapse (Kosten 1989). Studies should not be so long as to increase the likelihood of dropout, which is a highly likely event in drug-dependent populations. Twelve weeks seems to provide sufficient time to assess both stabilization and the possibility of relapse while on the drug.

Another critical factor in designing trials is to consider the latency of onset of clinical effect, which may take far longer than the study is designed or patients are able to remain in the study (Blaine et al. 1994). In some studies it has taken as long as 6 weeks for improvement to begin on SSRIs, while it often takes from 12 to 16 weeks to provide maximum benefit. It is especially difficult to include subjects with cocaine dependence in trials this long.

It is important to anticipate the problems of dropouts and to try to exclude unmotivated patients as well as those who are being pressured by others to enter into the program. Too many dropouts reduce the power of the statistical analysis and may leave a sample of patients that is unrepresentative of the group being studied. Special attention must be paid to the characteristics of dropouts not only in terms of demographic and clinical characteristics but also in terms of any kind of subtle clinical events that may have influenced their responses to treatment.

## PLACEBO-CONTROLLED STUDIES

There seem to be many open-label noncontrolled studies with positive results in the area of cocaine abuse. These results by and large are not substantiated when controlled studies are done (Satel and Kosten 1991). The state of the field, the urgency of finding a new drug, and perhaps the lack of standardized instruments no doubt contribute to these unreliable results.

The use of placebo is essential in studying a medication whose effects are as yet undetermined. The use of such a design reduces the numbers of patients required to demonstrate statistical significance between medication placebo and a known standard medication. Distinguishing active drug from placebo is often difficult because of a significant placebo response caused by too great a reliance on the patient's responses to the symptom cues that are given to elicit ratings, without sufficient attention being paid to the subtleties of symptoms and observation of the patient's behavior. Too much support of the patient, or encouragement of the patient to remain in a trial or psychosocial or psychotherapeutic support programs (which seem common in psychopharmacological trials for cocaine dependence) may also produce positive responses in patients who are generally believed to be highly susceptible to environmental and behavioral cues.

These positive responses may be particularly difficult to differentiate from positive responses to the medication.

## PSYCHOSOCIAL INTERVENTION

There is no doubt that cocaine dependence is a condition very much affected by nonmedical or social factors. This is perhaps what makes the condition responsive to psychosocial intervention, and as such the regular use of such methods to maintain compliance must be questioned in any clinical trial of a new medication for cocaine. While psychosocial intervention oftimes contributes to compliance and may clearly have beneficial effects on cocaine dependency, it is likely to confound the study of the efficacy of psychopharmacology and must be measured against the effectiveness of new medications rather than used to reinforce compliance with the program.

These interventions can mask drug effect. They can also enhance drug effect, as in methadone maintenance programs where psychotherapy has enhanced the efficacy of methadone treatment of heroin addicts while being essentially ineffective when used alone (Woody et al. 1983). The use of such approaches to ensure patient compliance needs to be weighed carefully and utilized only when the addition of such interventions is likely to bring out the beneficial effects of a less potent pharmacological treatment. However, there are problems in the use of such treatments especially in establishing a standardized method of treatment that can be uniform over time and among different therapists and multiple sites.

Given the sensitivity of the patient population and the fact that psychosocial interventions are often required to maintain patients in studies, it is important to keep asking the question of how various staff interactions with patients contributed to the patient's behavior and not simply assume that this is an area that does not need to be examined and that it can be assumed that there are no negative effects of staff attitudes and interactions on the patients.

## SUMMARY

Clinical trials require a quite distinct shift in attitudes and procedures from ordinary clinical practice insofar as they require a proactive approach to patient recruitment, enrollment, and followthrough as well as significant attention paid to issues of documentation, regulatory compliance, and error prevention. Take documentation, for example: Today's requirement to have an independent record of clinical events that are recorded on the case report forms was until 5 or 7 years ago not addressed in as much detail as it is today. This is one of the first adjustments that the new investigator must address. The researcher must keep looking to see what is missing from the location and procedures as a study takes place in order to create the necessary patient base for doing the study and ensuring that all needs necessary to produce the result are in place and that procedures are done with as few errors as possible. Everything must be done in conformance with good clinical practice and the standards set by the protocol. The researcher must be willing to deal with a world of breakdowns such as missing data, and the failure of the patient to revisit the office within the appropriate time dictated by the protocol and within the window of time or grace period allowed by the study. The researcher must ensure that the patients comply with the dosing schedule and that they are trained to return medications for accurate pill counts. And so on.

This means creating new procedures that are motivated by a commitment to producing a specific enrollment result defined by specific criteria and increasingly because of the press of time enrolled in a specific time period and put through a well-defined protocol process. Clinical research is dependent on a willingness to commit to a specific end result and do all that is necessary on a day-by-day basis to produce that result in terms of specific numbers, clean and accurate case report forms that are backed up by corroborating source documents in line with a specific timeline in which to accomplish the task, and an outreach effort to recruit and enlist patients, which may involve advertising and promotion of the program, all of which may contrast significantly with customary practice.

Clinical research involves reliance on additional dedicated personnel who are critical parts of the research team, including the telephone screening person who must be trained to follow a script and at the same time to be aware of the nuances of enrolling appropriate and compliant patients. The entire staff must be made part of the process and must work in concert to recruit and maintain the patient in a study while being aware of the effect these efforts may have on the placebo effect. It also requires considerable training, review, and constant communication among the staff to ensure that the complex coordination of numerous patients and procedures works smoothly.

There needs to be a willingness among the staff and the investigators to take correction from monitors who visit the site periodically and whose focus is on the quality of the data and not so much on the qualifications of the staff. This is not an action that people in nonresearch environments are trained to take.

Failure to appreciate the complexity of conducting clinical trials can contribute to much frustration to everyone involved. When there is understanding of all the variables that influence the ultimate results, there is a willingness to anticipate breakdowns and to turn breakdowns into opportunities to create new structures and develop new procedures that will ultimately facilitate a successful outcome.

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# Outcome Measurement Considerations: Pharmacological Treatments for Substance Abuse

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## INTRODUCTION

An extensive literature exists on outcome measurement for trials of treatments for psychiatric disorders. Less has been written specifically on outcome measurement for treatments for substance-related disorders; even less specifically for trials of pharmacological agents for substance disorders.

## OVERVIEW

Six questions are presented to systematically guide investigators' decisions on outcome assessment for randomized clinical trials of pharmacological agents for substance-related disorders (American Psychiatric Association 1994). Use of the questions is illustrated by applying them to cocaine dependence. The questions were distilled from four sources: the author's experience conducting psychiatric treatment outcome research, the extensive literature on treatment outcome methodology (Kazdin 1994), a recent comprehensive text on the clinical evaluation of psychotropic drugs (Prien and Robinson 1994), and Kraemer and Telch's (1992) paper on outcome measurement for clinical trials.

Because of the breadth of the existing relevant literature, a discussion of outcome measurement considerations for trials of pharmacological agents for substance-related disorders could result in a lengthy treatise. Instead, a strategy was adopted for this chapter to make it maximally useful with minimal length. The strategy is to articulate a conceptual framework (actually, a set of six questions) to guide investigators' decisions on outcome measure selection and related assessment issues for clinical trials of pharmacological agents for substance-related disorders. Along the way, a few pertinent, comprehensive references are provided.

## FRAME OF REFERENCE

The focus of this chapter is considerations relevant to answering the basic treatment outcome question: Does a pharmacological treatment have intended and clinically important effects on substance-related disorder(s) of interest? The discussion assumes that: (a) the measurement is to be done in the context of a randomized clinical trial (RCT), (b) the goal of the trial is to evaluate the efficacy of a pharmacological intervention for a substance-related disorder (e.g., as defined in the Diagnostic and Statistical Nomenclature of the DSM-IV, American Psychiatric Association 1994), and (c) a pharmacotherapy for adult outpatients is being examined. It is also assumed that the goal of the trial is explanatory rather than pragmatic (Lavori 1992). That is, the goal of the RCT is to draw conclusions about a treatment's causal effects on targeted outcomes.

Blaine and colleagues (1994) extensively discuss considerations relevant to designing clinical trials of pharmacological agents for substance-related disorders, including some of the particular problems (such as high attrition rates) associated with treatment efficacy trials for substance-related disorders. Moras (1993) discusses some of the outcome measurement problems that are unique to treatment trials for substance-related disorders, compared to trials for other common psychiatric disorders.

## GUIDING QUESTIONS FOR OUTCOME ASSESSMENT

Six basic questions can be used to guide investigators' decisions on outcome measures and related methodological issues for RCTs of pharmacological agents for substance-related disorders (see table 1). The questions apply equally to RCTs of other psychiatric disorders, but they are discussed and elaborated here for RCTs of substance-related disorders. The six questions were distilled mainly from four sources: the author's experience conducting psychiatric treatment outcome research, the extensive literature on treatment outcome methodology (e.g., Kazdin 1994; Kraemer et al. 1987; Lambert 1990; Lavori 1992; Rush et al. 1994), a recent comprehensive text on the clinical evaluation of psychotropic drugs (Prien and Robinson 1994), and an excellent paper by Kraemer and Telch (1992) on outcome measurement in clinical trials. Selected issues that pertain to answering each of the six questions are considered in the sections that follow.

**TABLE 1.** *The basic questions.*

1. What problems do cocaine-dependent individuals have?
2. Which of the problems is the treatment intended to address?
3. What outcomes associated with the treatment are of primary interest?
4. Which of the outcomes of primary interest can be measured *reliably* and *validly*?
5. How can investigators be sure that the pharmacological treatment of interest contributed substantially to the outcomes obtained?
6. How can researchers be sure not to miss outcomes associated with pharmacological treatments of interest?

NOTE: Questions 1 through 3 are adapted from Kraemer and Telch (1992).

### Step I: Identification of the Outcomes of Interest

Kraemer and Telch (1992) provide an exceptionally clear, yet sophisticated and comprehensive reference on outcome measurement for RCTs of psychiatric disorders. A systematic conceptual framework, in the form of three questions, is presented to guide investigators' selection of outcome measures. The questions are the first three in table 1. Kraemer and Telch (1992) illustrate and discuss the questions by applying them to mood disorders. However, the questions are appropriate for RCTs of other psychiatric disorders, including substance-related disorders. Once the three initial questions are answered, the investigator must evaluate and select (or develop, if necessary) measures to assess the outcomes of interest. "Outcomes" (see question 3, table 1) are features of a patient, such as frequency of drug use or frequency of associated high-risk activities such as use of dirty needles. Kraemer and Telch (1992) define an "outcome measure" as a procedure used "to obtain a number or classification from or about the patient that is indicative of the 'outcome' [of interest]" (p. 86).

The three questions are interdependent. As Kraemer and Telch (1992) point out, an "isomorphism" must exist between the disorder, the treatment that is being tested for the disorder, and the outcome assessment procedures that will provide an index of the usefulness of the treatment for the disorder. Moreover, the three questions logically precede other central decisions for RCTs (e.g., design, assessment intervals, analysis).

The initial three questions might seem straightforward. However, answering them is not necessarily straightforward, particularly when substance-related disorders are to be examined. Some considerations pertinent to answering the first basic question will be illustrated by applying it to cocaine dependence.

**Question 1. What problems do cocaine-dependent individuals have?**
*The perspective subquestion.* Answering the first question requires answering the subquestion, "From whose perspective?" Obviously relevant perspectives, using the criterion of parties with a vested interest in treatment outcomes, are: the cocaine abuser, the cocaine abuser's family and others with whom he or she has close personal ties, society, and the clinical investigator.

Answering the first basic question from different perspectives will yield different answers. Table 2 provides illustrative answers for cocaine dependence from three perspectives: cocaine abuser, society, and clinical investigator. The lists are not intended to be comprehensive. Their purpose is to illustrate the fact that different problems will be identified as central to a disorder, depending on the perspective from which the problems question is addressed. One obvious implication is that the outcome measures chosen will depend, at least partially, on an investigator's view of which perspectives are important.

*A key variable: Low subjective distress.* Problems 1 and 2 from the cocaine abuser's perspective (table 2) point to a key variable that must be considered when designing RCTs of substance-related disorders, in contrast to most other DSM-IV (American Psychiatric Association 1994) Axis I psychiatric disorders. The variable can be labeled in a variety of ways, e.g., "minimal subjective distress" or "low motivation to change." The point is that the symptoms that constitute DSM-IV diagnostic criteria for substance-related disorders often are not experienced as problematic by the person who meets the criteria for the disorder. In

**TABLE 2.** *Perspectives: What problems do cocaine abusers have?*

1. Cocaine user
    - a. None.
    - b. Feelings of euphoria, mastery, well-being, interest in life aren't frequent enough without use of cocaine.
    - c. Loss of energy needed to sustain use pattern.
    - d. Social reproach; dissatisfaction of family and others.
    - e. Loss of life satisfactions.
    - f. Fear of health effects.
2. Society
    - a. If intravenous user, can transmit HIV.
    - b. Poor performance in social roles (parenting, work).
    - c. Criminal behaviors.
    - d. Service overutilization (medical, incarceration, public assistance, foster care).
3. Clinical investigator
    - a. Features of cocaine use "syndrome."
        - Binges: repeated self-administration with larger and larger doses.
        - Withdrawal symptoms.
        - Craving.
        - Relapse.
    - b. Clinical depression.
    - c. HIV risk.
    - d. Poor quality of life even if stops drug use.
    - e. Activity of reward centers in brain.
    - f. Drug use maintained by operant and classical conditioning.

contrast to most other common DSM-IV Axis I disorders of adulthood, substance-related disorders often are not associated with subjective distress. In fact, the subjective experiences associated with drug use often are very positive: The experience typically is not just a neutral one of lack of subjective distress. The pleasure-producing or reinforcing effects of the "symptom" of substance use can be expected to compete with any associated negative effects or problems that could provide motivation for treatment.

The central relevance of this fact for outpatient RCTs of treatments for substance-related disorders is suggested by the high attrition rates in such studies (typically greater than 50 percent dropout in the initial phase of treatment). In fact, high attrition is one of the most robust findings from substance abuse treatment research to date. The fundamental problems posed by attrition to the interpretation of findings from RCTs are described by Howard and colleagues (1990).

Attrition in RCTs of substance-related disorders typically is substantially higher than in RCTs of other common disorders, such as mood and anxiety disorders. Attrition rates ranging from 20 percent to 40 percent generally are found in RCTs of mood and anxiety disorders (e.g., Elkin et al. 1989). Even attrition in the placebo control conditions of outpatient treatment studies of such disorders tends to be 40 percent or lower. The difference in attrition rates in RCTs of substance-related disorders and other psychiatric disorders typically is attributed to the relative lack of subjective distress and pleasurable effects associated with substance use which, in turn, reduces motivation for treatment.

What are the implications of the foregoing points for outcome measurement in RCTs of pharmacological treatments for substance-related disorders? One implication is that investigators should try to identify *problems* associated with the targeted substance-related disorder from the patient's perspective. The more able investigators are to find some source(s) of subjective distress associated with the disorder and the more effectively the pharmacological treatment, or the "treatment package" within which the pharmacological treatment is embedded, affects problems that are associated with subjective distress, the more likely that interpretable efficacy findings will be obtained (i.e., from a study with low attrition rates). A second implication of the low subjective distress feature is that society's perspective on the problems associated with a disorder is likely to exert more influence on outcome measure selection for substance-related disorders than for disorders in which the treated individual identifies the primary problems to be treated.

*A consideration: Outcomes assessed from different perspectives are likely to yield different findings.* The perspective subquestion is relevant to outcome assessment of pharmacological treatments in yet another way. A basic methodological conclusion from psychotherapy outcome research over the years is that outcomes typically differ depending upon the perspective from which outcome data are obtained, e.g., the patient, the therapist, an independent clinical evaluator, or a significant other (Strupp and Hadley 1977). The observation has led investigators to include outcome measures from multiple perspectives in studies, based on the premise that several perspectives typically must be recognized as valid when evaluating the state of a disorder. In other words, reasonably complete information on a treatment's efficacy requires outcome data from the perspectives that are most affected by, can provide expert opinions on, and/or can provide judgments that are less affected by the subjective biases inherent in the other important perspectives on the state of the disorder being examined.

*Other considerations: Necessary and sufficient conditions for defining a substance-related disorder, and the central role of society's perspective in evaluating outcomes.* The disorder of cocaine dependence also illustrates a point that is infrequently discussed when designing RCTs for substance-related disorders. The first basic question, "What problems do patients with the disorder have?" can confront investigators with the prominent role played by social values in the identification of substance use "disorders." For example, in a literature review prepared for the DSM-IV Substance-Related Disorders Workgroup, Irwin (1994) noted that "prior to the 1980's cocaine was considered to be a relatively safe, nonaddictive, euphoriant agent" (p. 169).

What are the scientific implications of the fact that society's opinions can change about what is and what is not problematic substance use? First, as already mentioned, society's perspective is a central one in identifying the problems associated with a substance-related disorder. Second, as recognized in the diagnostic criteria for substance-related disorders in the DSM-IV (American Psychiatric Association 1994), use of an illicit substance in itself does not merit being labeled a "disorder." Rather, certain patterns of use, i.e., patterns that are associated with functional impairment and/or high risk to oneself or others (in the absence of subjective distress), are required to be designated as a disorder.

The principle that the primary problems of substance users are *patterns* of use that are associated with functional impairment and/or types of risk to oneself or others is an important one for investigators to consider when choosing outcomes for pharmacological treatments for substance-related disorders. Conceptualizing the problem to be treated as a pattern of behavior (or use) will doubtless lead to different decisions about the most appropriate outcome measures and measurement strategies. Furthermore, the principle could affect investigators' decisions about which treatments or treatment packages merit testing in RCTs. For example, if a particular pharmacological agent targets only an isolated feature of use of a substance, such as craving or withdrawal symptoms, embedding the agent in a treatment package that consists of psychosocial interventions and, perhaps, other sequentially administered pharmacological agents, might be considered. For pharmacological agents that target narrow outcomes, a modular treatment package is likely to be needed to produce clinically significant outcomes in substance-related disorders, especially the outcomes of most interest from society's perspective.

**Question 2. Which of the problems is the treatment intended to address?** Possible answers to the second question, using the example of cocaine dependence, are shown in table 3. The answers there are based on a review of recent treatment studies for cocaine dependence and the discussion by Weiss and Mirin (1990). The table illustrates the kinds of problems and outcomes that currently tend to be examined in RCTs of cocaine dependence.

**Question 3. What outcomes associated with the treatment are of primary interest?** Table 4 presents examples of how the third basic question might be answered by investigators who want to examine a pharmacological treatment for cocaine dependence, based on current conventions in treatment research on cocaine use.

## Step II: Identification of Measures and Methodological Considerations

Once the first three questions have been answered, three more questions must be addressed to answer the basic treatment outcome question: Does pharmacological treatment X affect the desired outcomes for substance-related disorder Y? The next three questions are 4, 5, and 6 in table 1.

**TABLE 3.** *Question 2: Which of the problems is the treatment intended to address?*

1. Binge use (compulsive self-administration).
2. All use.
3. Withdrawal symptoms.
4. Craving.
5. Relapse.
6. Reward centers in brain.
7. Possible use-maintaining symptoms (e.g., depression).

**TABLE 4.** *Question 3: What outcomes associated with the problems are of primary interest?*

1. Reduced frequency of use.
2. Reduced amount of use.
3. Initial abstinence period (e.g., > 1 month).
4. Long-term abstinence.
5. Relapse prevention after a period of abstinence.
6. Less impairing or dangerous use pattern.
7. Less dangerous route of ingestion.

**Question 4. Which of the outcomes of primary interest can be measured *reliably* and *validly*?** Answers to the first three basic questions rely mainly on an investigator's conceptual skills, understanding of the disorder to be treated, knowledge of the potential effects of the treatment of interest, and value judgments. The next question requires psychometric expertise to answer. Reliability and validity (e.g., Guilford 1954; Kraemer and Telch 1992; Nunnally 1978) are the fundamental psychometric features of any measure that could be used to assess outcomes in RCTs. Simply defined, reliability refers to the repeatability of scores obtained on a measure. For scientific purposes, researchers want to know that the score or value assigned to a respondent based on a measure is a replicable index of his/her status on the measure at the time when the measurement was made. Psychometric methods for determining the reliability of a measure are designed to estimate the "true score variance" (e.g., compared to either random or nonrandom error variance) in a score on the measure. Alternatively stated, reliability statistics are estimates of the signal-to-noise ratio contained in scores on a measure. More reliable measures have more signal, less noise (error). Validity is the extent to which scores on a measure do, in fact, reflect the construct or variable that researchers think they do. An outcome measure's reliability and validity credentials are the fundamental determinants of the potential strength of the evidence (e.g., effect sizes) (Leon et al. 1995) and the accuracy of the conclusions (interpretation of the findings) obtained from an RTC.

Despite the linchpin importance of a measure's reliability and validity statistics, both tend either to be ignored or acknowledged only in superficial ways in psychiatric clinical outcome research. Well-established methodologies exist for the evaluation of a measure's reliability and validity (Nunnally 1978). Familiarity with the methods and knowledge of how to interpret reliability and validity statistics are required to choose between alternative measures to examine an outcome of interest. If an investigator does not have the required expertise, consultation on this aspect of measure selection should be sought.

A full discussion of reliability and validity evaluation of outcome measures is beyond the scope of this chapter. Only two additional points will be made here: One concerns a prominent error about reliability in psychiatric research and the other concerns the use of measures intended to circumvent self-report to evaluate drug use outcomes (e.g., urinalysis). Kraemer and Telch (1992), Leon and colleagues (1995), and Rush and colleagues (1994) provide additional discussion of reliability and validity of outcome measures, and of the critical need for psychometrically sound measure development for psychiatric treatment research.

*Reliability of observer-judged measures.* One of the most common investigator errors in published RCTs for psychiatric disorders is the belief that reliability inheres in observer-rated measures, such as the Hamilton Rating Scale for Depression (Hamilton 1960), the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D, Williams 1988), and the Structured Clinical Interview for DSM-IV Disorders (SCID, First et al. 1996). This belief is reflected in statements like "the SCID has been shown to have adequate reliability for the diagnosis of X." Such statements are sometimes followed by a kappa coefficient and a citation of a study that reported the kappa.

The reliability of scores on observer-rated instruments is always a function of both the instrument and the specific observer/user. Reliability-relevant features of observer/users typically include their clinical experience, both general and with the specific patient population being studied, and the training they received to use the instrument. Because reliability is never inherent in observer-judged instruments, reliability must be evaluated for every study. Figures from other studies in which other observers provided the data give no information whatsoever on the reliability of the data from the measures in the current study.

*Validity of self-report measures of drug use.* A second highly relevant point for outcome measurement in RCTs of substance-related disorders concerns the validity of self-report measures. It is commonly assumed by both investigators and clinicians who work in substance use treatment that self-report data on drug use during treatment cannot be relied upon as accurate. This concern has led to the standard utilization of other measures to evaluate drug use, i.e., measures that can circumvent dissimulation. To date, urinalysis is the most commonly used alternate method in RCTs of substance-related disorders.

Technical complexities associated with using urinalysis results to measure the outcome of reduced drug use are well detailed in several other chapters in this monograph and in Blaine and associates (1994). Less often considered are the psychological impacts and possible impact on attrition associated with the requirement to provide urine samples as part of a treatment program. Investigators of substance use treatments must closely consider (a) the probable validity of self-report measures of drug use and possible ways to enhance their validity (see Moras 1993), and (b) the benefits and costs (including low reliability and validity, and technical complexity) associated with methods that are designed to circumvent self-report indices of drug use.

**Question 5: How can an investigator be sure that the pharmacological treatment of interest contributed substantially to the outcomes obtained?** Answering this question requires sophistication and expertise in experimental design in general, the design of RCTs in particular, and careful attention to the implications of each design decision for the internal validity of the study (Cook and Campbell 1979). Internal validity refers to the extent to which a study's design, methods, and procedures allow the data obtained to be interpreted as evidence of the main hypothesis(es) being examined. The aforementioned edited volume by Prien and Robinson (1994) contains several chapters on relevant design and methodological issues, specifically for RCTs of pharmacological agents for substance-related disorders.

Table 5 presents an abbreviated list of pertinent design, methodological, and procedural questions that must be considered to plan an RCT that yields findings that can be interpreted as effects of a pharmacological agent on the outcomes of interest. All design considerations included in the list are discussed in chapters in Prien and Robinson (1994).

*Problems posed by adjunctive treatments.* Only one of the points listed in table 5, i.e., number 3, "Control and/or limit adjunctive psychosocial and pharmacological interventions," will be discussed here. The point concerns one of the most common sources of low internal validity in RCTs of treatments for substance-related disorders. The relevant principle is a simple one: Interpreting outcome findings as evidence for the efficacy of a treatment of interest requires, at minimum, that patients' receipt of other treatments is proscribed or somehow controlled.

Despite the logical necessity of the foregoing principle, patients in RCTs of treatments for substance abuse commonly receive many ancillary treatments and, even more problematic for the internal validity of a trial, often receive them on an as-needed (uncontrolled) basis. (Ancillary or adjunctive treatments are therapeutic or potentially therapeutic interventions that are not regarded by the investigators as part of the treatment[s] being examined.) Moreover, investigators often neglect to report any information on the ancillary treatments (e.g., what they were, what percentage of the patients in each treatment condition received each one, etc.). Failure to control ancillary treatments in an RCT will fundamentally compromise interpretation of any effects found as due to the pharmacological treatment of interest.

**TABLE 5.** *Question 5: How can researchers be sure that the pharmacological agent contributed substantially to the outcomes?*

1. Pretrial "lead-in" placebo washout phase.
2. Placebo control condition in design.
3. Control and/or limit adjunctive psychosocial and pharmacological interventions.
4. Control use of substances.
5. Assess compliance with the pharmacological treatment.

*Substance-related disorders are maintained by multiple variables.* A common rationale for providing ancillary treatments to patients in substance disorder treatment studies is that the patients have multiple problems (Moras 1993). Furthermore, it is often argued that the treatment of interest is unlikely to be efficacious if the patients' other problems are not also addressed. Oddly, when the latter statement is made, it is not linked to the logical implication that the findings of the study cannot be interpreted as evidence for the treatment being examined alone: The efficacy data necessarily pertain to the entire treatment package within which the treatment of interest was (sometimes naturalistically) embedded.

The foregoing points are likely to be particularly relevant for RCTs of pharmacological agents for substance disorders. Many experienced substance abuse treatment investigators hypothesize that substance-related disorders are caused and/or maintained by a network of variables, with psychosocial factors playing a substantial role in maintaining, if not causing, patterns of substance abuse. Such hypotheses, plus the commonly acknowledged limitations in the efficacy of methadone, the most efficacious pharmacological intervention for a substance-related disorder to date, have obvious implications for the development of other pharmacological interventions. They suggest that efforts to develop other pharmacological agents for substance disorders will be limited unless the interventions are provided in the context of more comprehensive treatment packages or programs.

*Need for multicomponent treatments.* What do the preceding arguments suggest about the development of new pharmacological treatments for substance-related disorders? One implication is that investigators are well advised to consider the range of problems associated with the disorder of interest, which aspects of the disorder the pharmacological agent can reasonably be expected to affect, and other interventions that might be needed in conjunction with the pharmacological agent to attain clinically significant outcomes. Another implication is that pharmacological agents that are intended to have only narrow effects (e.g., on craving) might be most cost-effectively examined in basic research studies with human beings; then, if efficacious, included as a component of a more comprehensive treatment. The comprehensive treatment would then be examined in an RCT, not the pharmacological treatment alone. The National Institute on Drug Abuse's Behavioral Therapies Development Program (1994) provides an incentive for the development of such treatment packages.

**Question 6. How can researchers be sure not to miss outcomes associated with a pharmacological treatment of interest?** Similar to question 5, answering this question requires sophistication in experimental design. It also requires expertise in the conduct of pharmacological treatment trials, particularly knowledge of variables that affect the effects of pharmacological agents. Table 6 lists a few central considerations for answering this question. The points listed will be discussed briefly. The reader is referred again to the comprehensive edited text by Prien and Robinson (1994) with chapters on the relevant considerations.

The first two points in table 6 concern a topic previously discussed, the severe compromise posed by high attrition to obtaining interpretable efficacy findings from an RCT. Point 1 in table 6, matching the outcome goals of patients who have the substance disorder to be treated with the probable effects of the treatment, will reduce attrition as long as the treatment itself is not unduly noxious in some way. The second point, "stability of the patient's motivation for the goal," also relates to attrition concerns, but is focused on sample selection. Comorbid psychiatric disorders and comorbid substance-related disorders are examples of variables that can undermine the stability of patients' motivation for a treatment that they actually endorse. Therefore, the presence of such comorbid conditions can increase attrition. On the other hand, adding exclusion criteria to sample selection criteria can compromise a study's external validity, i.e., the generalizability of the results.

**TABLE 6.** *Question 6: How can researchers be sure not to miss outcomes associated with the pharmacological agent?*

1. Patient goal and treatment goal matching.
2. Stability of patient's motivation for goal.
   a. Polysubstance abuse
   b. Comorbid psychiatric diagnoses
3. Reliable measures.
4. Variables that affect pharmacokinetics and pharmacodynamics.
5. Optimal psychosocial treatment "context" for pharmacological agent.
6. Statistical analyses.

Point 3 highlights the role of reliable measures in obtaining scores that have minimal error variance which will, in turn, increase the probability of finding desired outcomes if they are, in fact, effected by a treatment. Point 4 highlights the fundamental importance of using knowledge of the pharmacokinetics and pharmacodynamics of a pharmacological agent (Greenblatt et al. 1994) in design and sampling decisions for an RCT. Needed knowledge of this type ideally will be generated in preparation for an RCT so that it can be used in designing the RCT. Such knowledge is a central determinant of the effects that will be found in an RCT of a pharmacological agent. The knowledge is equally as central to the findings as are the reliability and validity of the outcome measures. For example, knowledge of gender differences associated with pharmacokinetics, such as the impact of the menstrual cycle, is critical information for planning RCTs of agents intended to be used with both male and female substance users.

The earlier section of this chapter on basic question 5 (table 1) also is relevant to point 5 in table 6. A pharmacological intervention might be capable of potentiating a desired effect, but will do so only if other aspects of a patient's substance-related disorder also are treated in some way. Point 6 highlights the importance of using appropriate statistical techniques intelligently (Lavori et al. 1994). Also, new and sophisticated statistical procedures are being identified that can be applied to RCTs. For example, random regression (Gibbons et al. 1993) might be productively applied to evaluate and compare the rates of change of various outcomes associated with different treatments when repeated measures of outcomes are obtained.

## CONCLUDING REMARKS

This chapter was intended to be concise, despite the broadness and complexity of the topic. Thus, main points will not be summarized here. Rather, for a summary, refer to table 1, which contains six basic questions for planning outcome assessment for RCTs of pharmacological agents for substance-related disorders. As noted, the six questions are equally applicable to RCTs of other common psychiatric disorders. For more information on any of the questions, the reader should turn to the relevant section of the text.

One potentially controversial point made here is that investigators who are interested in developing and examining pharmacological agents for use in the treatment of substance-related disorders are encouraged to closely consider the requisite psychosocial treatment "context" for optimal delivery of the agent of interest, i.e., the context that is needed for the agent to be associated with clinically significant effects. This point was made based on the relative lack of highly efficacious treatments for substance-related disorders, either pharmacological or psychosocial, despite many years of research effort. The difficulty in developing treatments with the desired levels of efficacy has led many experienced substance abuse researchers to posit a complex network of maintaining variables that, even if not causative, make strong contributions to the continuation of substance-related disorders in adults. The preceding speculation, in turn, is associated with a clear current trend to recommend the development of comprehensive treatment packages for substance-related disorders, including treatments that combine psychosocial and pharmacological components.

A final point to be made is that a considerable amount of knowledge has been amassed over the years on the conduct of RCTs for psychiatric disorders. This knowledge is well illustrated in several references that were cited such as Kazdin (1994), Kraemer and Telch (1992), and the chapters in Prien and Robinson (1994). As alluded to by Kraemer and

Telch (1992), one of the main problems now faced in generating interpretable findings from RCTs is the failure of many investigators to *implement* available knowledge (e.g., about the central importance of selecting reliable and valid outcome measures). One contribution to this problem, perhaps, is the incentive system that affects investigators who work in university settings. Promotion typically is largely contingent on number of publications, rather than their quality. In addition, designing and conducting rigorous studies is more labor intensive than completing weaker studies. The time and effort involved in a rigorously done study also can be associated with longer time to publication and, perhaps, fewer publications. Investigators interested in pharmacological treatments for substance-related disorders who have been strongly influenced by standards applied in many pharmaceutical company-sponsored trials might be especially susceptible to design and methodological "shortcuts." In any event, the point to be made is that much sophistication now exists about the critical considerations for, and necessary elements of, interpretable RCTs. This sophistication is ready to be applied to pharmacological treatments for substance-related disorders.

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# Variability in Treatment-Seeking Cocaine Abusers: Implications for Clinical Pharmacotherapy Trials

*Kathleen M. Carroll, Charla Nich, and Bruce J. Rounsaville*

Variability in cocaine abusers seeking treatment in terms of potential prognostic dimensions such as severity of dependence, route of administration, concurrent use or dependence on other drugs and alcohol, psychiatric comorbidity, treatment history, and many others, has been a long-recognized feature of this population. Consideration of heterogeneity among cocaine abusers is important as it may point to treatment strategies for some subpopulations. For example, identification of subgroups with distinct clinical characteristics or who have differential response to treatment is useful, as it may point to specialized treatment strategies that may be effective for these subgroups or for patient-treatment matching. At the same time, however, patient heterogeneity often confounds the interpretation of data from many pharmacology and psychotherapy treatment trials conducted thus far, by introducing noise and decreasing power to detect treatment effects.

In considering the implications of patient variability for cocaine pharmacotherapy trials, it should first be noted that no pharmacotherapies are universally effective. For example, methadone maintenance, by far the most effective treatment for opioid dependence, is not universally successful in retaining patients or affecting complete cessation of illicit opioid use (Lowinson et al. 1992). Although program characteristics are associated with a great deal of variability in outcome (Ball and Ross 1991), patient characteristics such as psychiatric severity is another important predictor of response to methadone maintenance treatment (McLellan et al. 1993; Rounsaville et al. 1982). Similarly, although naltrexone has had limited impact on the drug abuse treatment system because of compliance and retention issues, it nevertheless retains a place in the treatment system because it is successful with some types of patients, typically middle-class patients and those with less severe or less chronic opioid dependence (Rounsaville 1995). Thus, success profiling, i.e., identifying patient characteristics associated with optimal outcome in well-defined treatments, is an important strategy for enhancing the effectiveness of treatment by providing treatment primarily to those most likely to benefit from it. Evaluation of patient-treatment interactions has become a cornerstone of research on psychosocial treatments for substance dependence, where main effects of one form of treatment over another are rare, and response to even the most effective psychosocial approaches is incomplete. Evaluation of patient-treatment interactions may be an underutilized strategy in medications development.

To illustrate how evaluation of variability in treatment response as a function of patient characteristics may lead to a more complete understanding of a treatment's effects and help make sense of apparently contradictory findings across different studies, two examples from recent clinical trials evaluating pharmacotherapy for cocaine dependence will be presented. The first example illustrates variations associated with patient characteristics as moderators of treatment response (variables that affect the strength or direction of treatment response); the second illustrates implications of a patient characteristic as a mediator of treatment response (a mediator is a variable that produces a relationship between the independent and dependent variable). In other words, mediators determine the nature or mechanism of a matching effect, and moderators determine the strength of a match (see Baron and Kenny 1986, and DiClemente et al. 1994 for a fuller description).

## Example 1: Desipramine Treatment of Cocaine Dependence

Enormous excitement was generated by the initial promising findings concerning the effectiveness of tricyclic antidepressant treatment of cocaine dependence, first in an open trial (Gawin and Kleber 1984) and later in a randomized, double-blind, controlled trial (Gawin et al. 1989), which indicated significant reductions in cocaine use for desipramine compared to lithium and placebo. However, later studies conducted in other settings with different patient populations generally failed to find main effects supporting the effectiveness of desipramine among the general population of cocaine abusers, including those on methadone maintenance (Arndt et al. 1992; Kosten et al. 1992; Weddington et al. 1991). What happened? While this set of studies underlines the importance of replicating a treatment's effects in multiple studies before it is widely adopted, it also highlights the point that variations in a medication's effectiveness may be explained by the changing nature of the patient population.

To illustrate this, findings from the Gawin study will be compared with outcomes from a later randomized controlled trial of desipramine and cognitive-behavioral relapse prevention, in a 2X2 design, as treatment for 121 cocaine abusers (Carroll et al. 1994*a*). This study was conceived in part as a replication of the initial promising findings of desipramine, but more importantly to extend those findings by systematically evaluating the effectiveness of psychotherapy as well. Therefore, the authors strove for a high level of methodological rigor in specifying and implementing both pharmacologic and psychotherapeutic aspects of treatment. For example, design features of the study included:

- Random assignment to treatment condition (desipramine plus relapse prevention treatment, desipramine plus clinical management, placebo plus relapse prevention, or placebo plus clinical management.
- Careful selection of appropriate control conditions for both the desipramine treatment (placebo) and the cognitive-behavioral psychotherapy (clinical management, which provided nonspecific aspects of psychotherapy but not active ingredients of the coping skills treatment).
- Specification of all aspects of treatment delivery in manuals (Carroll et al. 1991*b*; Fawcett et al. 1987).
- Adequate duration of treatment (12 weeks) to allow emergence of specific effects of both pharmaco- and psychotherapy.
- Avoiding confounding of treatment through limiting subjects' exposure to nonstudy treatments.
- Delivery of treatments by experienced therapists committed to the type of treatment they conducted (doctoral-level psychologists conducted the cognitive-behavioral relapse prevention treatment, and postresidency psychiatrists conducted clinical management).
- Extensive therapist training, which included both a 2-day didactic seminar and successful completion of at least one closely supervised training case.
- Efforts to improve adherence to manual guidelines and prevent drift through the main phase of the study, which included regular meetings with therapists in each condition to discuss case material and review session videotapes.

- Close monitoring of both forms of treatment, which included regular assessment of medication plasma levels and process assessment of session videotapes by independent raters, which showed the relapse prevention and clinical management treatments were discriminable (Carroll et al., in press).

- Multidimensional assessment of outcome from multiple sources, including clinical evaluators blind to treatment condition (Carroll et al. 1994*a*).

- 1-year followup, where 80 percent of all patients randomized to treatment were interviewed at least once (Carroll et al. 1994*b*).

## Results: Main and Interaction Effects

After 12 weeks of treatment, subjects as a group showed significant improvement on most outcome measures, including cocaine use and psychosocial outcomes. However, significant main effects of desipramine, relapse prevention, or their interaction were not seen on primary outcomes, which included urine toxicology screens, frequency of cocaine use in the past 30 days, and Addiction Severity Index (ASI) cocaine composite scores (see Cacciola et al., this volume). Therefore, despite the authors' clinical sense of marked variations in outcome among patients in the sample, outcomes appeared similar across treatments when the sample was evaluated as a whole. However, there were data from two previous studies suggesting that severity may be an important moderator of treatment response in cocaine abusers. Therefore, by not evaluating outcome with respect to severity differential treatment effects may be masked. The first of these studies reported on a 1-year followup from a diagnostic study of 298 treatment-seeking cocaine abusers (Carroll et al. 1993*b*), which found that the most consistent and robust predictor of functioning was the subjects' severity of cocaine dependence at baseline (as assessed by total number of DSM-III-R cocaine dependence criteria endorsed). The second study, pointing to severity as a moderator of treatment response in cocaine abusers, was a pilot psychotherapy study that compared two forms of psychotherapeutic treatments: cognitive-behavioral relapse prevention (RP) or interpersonal psychotherapy (IPT) (Carroll et al. 1991*a*). In that study, while again there were no main effects of psychotherapy type on cocaine outcomes, marked differences in response to treatment were found after stratifying for baseline severity: At low levels of severity subjects both IPT and RP fared about equally in achieving at least 3 weeks abstinence during treatment.

However, at high levels of severity, subjects in RP were significantly more likely to attain 3 weeks of abstinence than high-severity patients treated with IPT (54 percent versus 9 percent).

Thus, as previous research suggested that severity of cocaine use may be an important moderator of treatment response in cocaine abusers, data from the relapse prevention-desipramine study evaluating interactions of treatment type by severity were reanalyzed. However, severity was not defined a priori as a factor. The sample was stratified into three levels (to sharpen contrasts between high and low severity use): low (1 to 2.5 g of cocaine per week at baseline), moderate (2.6 to 4.4 g per week), and high severity (more than 4.5 g per week). Univariate ANOVAs indicated this classification of severity was associated with other indicators, including chronicity of use and route of administration.

Results of the exploratory 2X2X3 (medication by psychotherapy by severity) ANOVAs are illustrated in figure 1. There were consistent severity by psychotherapy (relapse prevention versus clinical management) interactions, with higher severity subjects who received relapse prevention reporting significantly longer consecutive periods of abstinence, better retention, and fewer cocaine-positive urine toxicology screens.

There were no significant pharmacotherapy (desipramine/placebo) by severity interactions for primary outcomes for the full sample. However, for the subsample that completed at least five sessions and therefore had greater opportunity for emergence of medication effects, there was a significant interaction between medication and baseline severity. Low-severity subjects treated with desipramine had significantly longer periods of consecutive abstinence than low-severity subjects taking placebo; for moderate and high-severity subjects desipramine and placebo were comparable in effectiveness.

## Comparison With Other Desipramine Studies

Thus, in this study desipramine appeared most effective among the least severe cocaine abusers. These findings were thus inconsistent with the data reported by Gawin and colleagues (1989), which suggested a robust main effect for desipramine. As these two studies were conducted in the same clinic, by overlapping groups of investigators, using parallel sets of procedures and inclusion/exclusion criteria, the differences in desipramine effects is puzzling, until characteristics of the two samples are compared: Subjects in the Gawin and colleagues 1989 study were

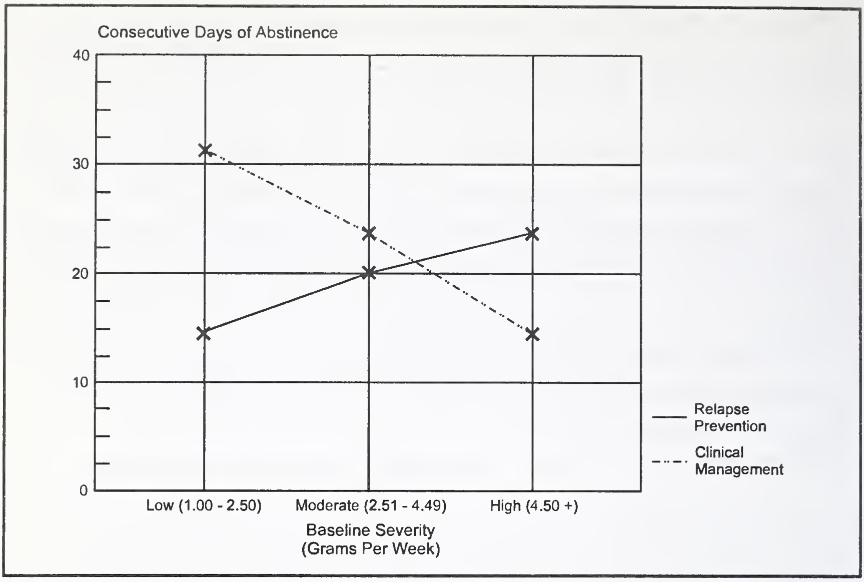

**FIGURE 1.** *Severity by psychotherapy interaction.*

KEY: Abstinence initiation in treatment N = 110.

recruited between 1984 and 1987 during the burgeoning of the cocaine epidemic, while the Carroll and colleagues 1994 study recruited patients between 1987 and 1991, a period characterized by rapid shifts in the treatment-seeking population and increasing predominance of freebase and crack use.

As indicated in table 1, the two subject samples differed on a number of dimensions. The Gawin sample included fewer blacks and Latinos, more patients who were employed, and more intranasal and fewer freebase users. Subjects in the Gawin sample also reported using fewer grams of cocaine per week on average, and had approximately half the rate of Axis I disorders with respect to the Carroll and colleagues 1994 study. Thus, it appears that subjects in the Gawin study, which suggested the general effectiveness of desipramine, were most similar to the less severe subsample of the authors' study (the only subgroup for which desipramine was found to have an effect on cocaine use). Similarly, Arndt and associates (1994) reported a desipramine effect among methadone-maintained cocaine abusers only when those with concurrent antisocial personality were excluded. Antisocial personality disorder has been associated with severity of cocaine abuse (Carroll et al. 1993*a*). Thus, exclusion of those with antisocial personality disorder in

**TABLE 1.** *Variations in sample characteristics, Gawin et al. (1989) compared to Carroll et al. (1994a)*

| Characteristic | Gawin et al. (N = 72) | Carroll et al. (N = 121) |
|---|---|---|
| Percent female | 24% | 27% |
| Percent white | 76% | 46% |
| Percent employed | (mean 10 yr) | 52% |
| Percent single/divorced | 71% | 71% |
| Mean age | 29 | 29 |
| Mean cocaine g/wk | 3.6 | 4.4 |
| Route of administration | | |
| Percent intranasal | 50.0 | 29.0 |
| Percent freebase | 32.0 | 62.0 |
| Percent intravenous | 18.0 | 9.0 |
| Lifetime rates, DSM-III-R psychiatric disorders | | |
| Any Axis I disorder | 14% | 26% |
| Any affective disorder | 11% | 20% |
| Any anxiety disorder | * | 13% |
| Antisocial personality | * | 49% |
| Alcohol dependence | * | 33% |

NOTE: * Indicates not reported.

the Arndt and colleagues 1994 sample may have left a less severe subsample that, like the less severe sample in the authors' study, was more responsive to desipramine treatment.

## Example 2: Desipramine Treatment of Depressed Cocaine Abusers

The growing literature on desipramine treatment of cocaine dependence provides another example of how variations in sample characteristics across studies may influence conclusions about a medication's effectiveness. Recall that there are two principal rationales for antidepressant treatment of cocaine dependence, each targeted to different groups. First, desipramine may reverse cocaine-induced disregulation in reward mechanisms, hence cocaine craving and use, in the general population of cocaine abusers (Gawin and Kleber 1984; Gawin et al. 1989). The example above suggests that severity may be a moderator of this effect. However, a second rationale for desipramine is that it may work through treating depression in the subgroup of cocaine abusers who may be attempting to self-medicate depressive symptoms (see Kosten 1989). Here, the presence of depression would serve as a mediating variable for desipramine effects (e.g., desipramine would work only for depressed subjects and reduction in depression would lead to reductions in cocaine use). This distinction is also important in relation to the inconsistent reports of the effectiveness of antidepressant treatment for cocaine abusers across studies, as variations in rates of depression across studies could affect conclusions about desipramine's effectiveness if it exerted effects primarily through an antidepressant mechanism or was differentially effective with depressed cocaine abusers (Carroll et al. 1995).

However, few studies have reported on the effectiveness of antidepressants in reducing both cocaine use and depressive symptoms, or on differences in desipramine's effectiveness for general (nondepressed) versus depressed subpopulations. Giannini and colleagues (1986) reported a significant reduction in depression for cocaine addicts treated with desipramine in an open trial, but did not report on cocaine outcomes. As mentioned earlier, Gawin and colleagues (1989) reported that desipramine significantly reduced cocaine use regardless of whether patients were depressed. Weddington and colleagues (1991) found no effect of desipramine over placebo on either cocaine or depression outcomes; however, in that study, desipramine doses may have been subtherapeutic. Among methadone-maintained opioid addicts who also abused cocaine, Arndt and colleagues (1992) reported that desipramine improved psychological functioning but did not affect cocaine use. Ziedonis and Kosten (1991) found that depressed methadone-maintained opiate addicts showed significant reduction in cocaine use when treated with amantadine or desipramine compared with placebo, although these medications were not effective in reducing cocaine use for nondepressed subjects. They also reported that neither desipramine nor amantadine reduced depressive symptoms significantly, a small increase in depressive symptoms was seen for those treated with placebo.

In the 1994 study, the rationale for use of desipramine was as an anticraving agent, intended to facilitate abstinence initiation in a heterogeneous sample of cocaine users. Thus, the initial analyses did not evaluate either (a) the effectiveness of desipramine as an antidepressant agent for depressed cocaine abusers, or (b) whether desipramine might have greater efficacy in reducing cocaine use among depressed patients.

The data were therefore reanalyzed to address these issues. For these analyses, treatment response was assessed based on level of current depressive symptoms (rather than presence of a DSM-III-R depressive disorder) for several reasons: First, diagnosing affective disorders in current substance users is complicated because it is difficult to distinguish transient, substance-induced symptoms from more enduring syndromes (Meyer 1986). Second, stringent guidelines for diagnosing affective disorders in cocaine users, which require a period of stable abstinence before symptoms can be counted as meeting criteria for affective disorders, may underestimate rates of depressive disorders in current cocaine abusers (Rounsaville et al. 1991). For example, although subjects' mean pretreatment Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HRSD) scores were 9.03 (SD = 6.36) and 7.66 (SD = 5.64), respectively, only 1 subject met criteria for a current and 17 (20.7 percent) for a lifetime diagnosis of major depressive disorder. This was in large part due to these subjects' chronic substance use histories, which typically began in early adolescence, with few periods of stable abstinence that would allow definitive assessment of psychiatric symptomatology independent of drug effects.

Thirty-seven subjects (35 percent) were identified as having at least mildly elevated depressive symptoms at baseline, defined by BDI scores of 8 or above, and HRSD scores of 7 or above. Beck identified a score of 8 or above as consistent with moderate depression (Beck and Beck 1972). While the HRSD has no standard scales for interpretation, Frank has proposed a cutoff of seven to indicate presence of partial or full expression of depression (Frank et al. 1991). The combination of the two criteria was used to provide a more reliable indicator of level of depressive symptoms and to identify a sample where independent evaluators' clinical impressions were consistent with patient self-reports of depressive symptoms. Compared to the 72 subjects who did not meet these criteria for elevated depressive symptoms, the 37 depressed subjects were significantly more likely to be female and white, which is consistent with recent studies evaluating gender (Griffin et al. 1989) and race (Ziedonis et al. 1994) differences in clinical samples of cocaine abusers. As expected, depressed subjects were significantly more likely to have a lifetime history of a major depressive episode (36 percent versus 15 percent). There were no differences between the depressed and nondepressed groups in terms of marital status, education, socioeconomic status, or treatment group assignment. Regarding severity of cocaine use, there were no differences between the depressed and nondepressed groups on frequency or quantity of cocaine use nor principal route of administration. However, the ASI cocaine composite score (see Cacciola et al., this volume) suggested significantly higher severity for the depressed group. Because of the baseline differences between depressed and nondepressed subjects with respect to ASI cocaine composite scores and gender, the analyses described below were repeated controlling for these two variables. Neither gender nor baseline cocaine use had a significant main effect on cocaine or depression outcomes, nor did controlling for these variables alter the patterns or significance of the findings presented below.

## Treatment Response in Depressed Versus Nondepressed Cocaine Abusers

Depressive symptoms dropped significantly more for the depressive subgroup than the nondepressed subgroup as measured by both the BDI and the HRSD, regardless of treatment condition. As shown in table 2, although the depressed subjects were comparable to or more severe than the nondepressed users on baseline measures of cocaine use, regardless of treatment condition, the depressed subjects tended to accrue more days of consecutive abstinence than nondepressed subjects (25.1 versus 18.8 days, NS), and reported a higher percentage of abstinent days (0.86 versus 0.81, NS), although these differences were not statistically significant.

Table 2 also shows that depressed subjects treated with desipramine had a significantly greater reduction in depressive symptoms than placebo-treated depressed subjects, as measured by the BDI ($F = 3.80$, $p < 0.05$). Desipramine-treated subjects had a significant reduction in depressive symptoms, as measured by the HRSD, regardless of whether or not they were depressed ($F = 3.37$, $p < 0.01$). Relapse prevention treatment was not associated with greater reduction in depressive symptoms than clinical management for either the whole sample or the depressed subgroup.

For cocaine outcomes, desipramine was not associated with significant improvements over placebo for either the full sample or the depressed subgroup. However, there was a significant interaction for psychotherapy type and depression on some cocaine outcomes. Depressed subjects treated with relapse prevention reported significantly more days of consecutive abstinence than the depressed subgroup, which received clinical management (30.3 versus 20.2 days), while nondepressed

**TABLE 2.** *Cocaine and depression outcomes by treatment group ($N = 109$).*

| | Treatment Group[1] | | | | | Significance | |
|---|---|---|---|---|---|---|---|
| | CM/DMI N = 25 | RP/DMI N = 28 | CM/PLA N = 27 | RP/PLA N = 29 | Overall mean | Main Effects | Interaction |
| Number of psychotherapy sessions[2], mean (sd) | | | | | | | |
| Euthymic | 7.6 (3.3) | 6.4 (3.9) | 7.2 (3.7) | 6.5 (3.5) | 6.9 (3.6) | | |
| Depressed | 5.9 (3.2) | 10.2 (2.8) | 6.3 (2.9) | 9.5 (4.0) | 7.9 (3.6) | | RP/DEP[3] |
| Cocaine Outcomes | | | | | | | |
| Consecutive days of abstinence, mean (sd) | | | | | | | |
| Euthymic | 28.4 (27.6) | 14.1 (11.9) | 20.1 (15.5) | 14.9 (11.9) | 18.8 (11.9) | | |
| Depressed | 19.0 (18.7) | 30.6 (19.1) | 21.9 (26.2) | 29.7 (24.7) | 29.7 (24.7) | | RP/DEP[3] |
| Percent days abstinent[4], mead (sd) | | | | | | | |
| Euthymic | 0.84 (0.15) | 0.82 (0.14) | 0.79 (0.23) | 0.81 (0.19) | 0.81 (0.18) | | |
| Depressed | 0.85 (0.12) | 0.91 (0.06) | 0.83 (0.11) | 0.86 (0.15) | 0.86 (0.10) | | |

KEY: 1 = CM = clinical management, DMI = desipramine, RP = relapse prevention, PLA = placebo, DEP = depression; 2 = Range is 1 to 12; 3 = Indicates significant ($p < 0.01$) interaction of psychotherapy condition with depression; 4 = Indicates percent days abstinent as percentage of total days in treatment; 5 = Indicates significant ($p < 0.05$) interaction of desipramine and depression.

**TABLE 2.** *Cocaine and depression outcomes by treatment group (N = 109) (continued).*

| | Treatment Group[1] | | | | | Significance | |
|---|---|---|---|---|---|---|---|
| | CM/DMI N = 25 | RP/DMI N = 28 | CM/PLA N = 27 | RP/PLA N = 29 | Overall mean | Main Effects | Interaction |
| Depression Outcomes | | | | | | | |
| Beck Depression Inventory | | | | | | | |
| Euthymic | | | | | | | |
| Pretreatment | 5.6 (4.9) | 7.8 (6.6) | 6.4 (5.7) | 5.9 (4.7) | 6.4 (5.4) | | |
| Posttreatment | 1.7 (2.5) | 50. (6.9) | 2.7 (3.2) | 4.2 (6.0) | 3.7 (5.6) | | |
| Depressed | | | | | | | |
| Pretreatment | 13.7 (4.5) | 11.8 (3.8) | 17.1 (5.5) | 15.8 (4.0) | 14.2 (4.7) | Time | |
| DMI/DEP[5] | | | | | | | |
| Posttreatment | 4.3 (4.2) | 3.8 (3.8) | 10.6 (10.6) | 4.8 (8.7) | 6.2 (7.0) | DEP | DEP/Time |
| Hamilton Rating Scale for Depression | | | | | | | |
| Euthymic | | | | | | | |
| Pretreatment | 5.6 (3.0) | 5.2 (5.2) | 5.4 (5.4) | 4.9 (3.4) | 5.2 (4.2) | | |
| Posttreatment | 3.2 (3.0) | 4.6 (5.6) | 4.5 (3.3) | 5.1 (4.0) | 4.4 (4.1) | | |
| Depressed | | | | | | | |
| Pretreatment | 11.4 (3.8) | 13.4 (7.0) | 12.9 (5.1) | 10.3 (3.0) | 12.2 (5.2) | Time | DMI/Time |
| Posttreatment | 5.4 (3.7) | 3.1 (2.4) | 9.8 (6.4) | 6.0 (5.9) | 5.7 (4.9) | DEP | Dep/Time |

subjects accrued more abstinence in clinical management (23.7 versus 14.6 days, F = 6.95, $p < 0.01$). While this pattern was also seen for percent days abstinent during treatment, the interaction was not statistically significant.

Thus, analyses of desipramine effects on depressed cocaine users suggested that desipramine was an effective antidepressant in this sample, but appeared to have little effect on cocaine use. There were, however, moderate correlations between reductions in depressive symptoms and cocaine use (range 0.20 to 0.35). The direction of the moderate cocaine depression relationship could not be determined from the data; that is, whether reductions in cocaine use led to improvements in depression or reduction of depression made it easier for patients to reduce their cocaine use or both. That these correlations were higher for patients who received desipramine compared to placebo suggests that the early but transient desipramine-associated reductions in cocaine use may have been associated with an antidepressant effect. To evaluate these relationships further and to explore the role of depression as a potential mediator of desipramine effects, further research, particularly desipramine trials that specify depression as an a priori matching variable (such as those described by Nunes, this volume) are needed.

## RECOMMENDATIONS

Currently there is no medication that has been shown to be broadly effective for retaining cocaine abusers in treatment, nor in reducing their cocaine use. However, as illustrated in these two examples, there is growing evidence that available treatments may be more effective in some subgroups of cocaine abusers. Thus, rather than abandon current approaches because of their apparent modest effects in treating the general population of cocaine abusers, a more fruitful strategy may be identification of characteristics associated with differential response to treatment (that is, it may be better to effectively treat some cocaine abusers some of the time than no cocaine abusers none of the time). A crucial advance in this process would be more careful assessment and description of study samples, as well as examination of outcome variability as a function of selected patient characteristics. Moreover, a thorough description of study samples in terms of clinically important and theoretically relevant features would also provide an important means of facilitating comparison of outcomes across different studies conducted by different investigators.

A small set of potential moderating variables is listed below. First, however, it is important to note that in evaluating identifying matching variables, investigators much be cautious about collinearity among matching variables. Many key prognostic variables may be moderately to highly correlated among clinical samples of cocaine abusers. For example, as noted earlier, the data suggested that depression was associated with differential response to psychotherapy and pharmacotherapy; however, several other variables, particularly gender and race, were significantly associated with depressive symptomatology. Although our findings held even when controlling for these variables, it was not completely clear whether it was the presence of depressive symptoms, or another related variable, that was responsible for the observed interactions. Thus, in many cases it will be unclear whether it is the identified matching variable, or another correlated variable, that was responsible for the "match." Therefore, it should be noted that in the following list some variables may be highly associated with others.

1. *Gender.* While few studies have found gender effects in treatment response (McLellan et al. 1994), in most studies conducted to date, samples of women have been too small to conduct analyses of gender effects with adequate power. Female cocaine patients may differ from males on a number of clinically relevant variables that may be associated to outcome and treatment response (Griffin et al. 1989), including severity and chronicity of cocaine use, psychopathology, and social and family support.

2. *Race.* Some studies have found race to be a prognostic variable (Grabowski and Higgins 1992) for medication response in cocaine abusers. However, it is not yet clear to what extent characteristics associated with race in specific samples (e.g., socioeconomic status, source of referral, social supports) may account for apparent race effects.

3. *Education and employment status.* Education and employment have been among the more consistent predictors of treatment retention and response in the drug abuse treatment literature. Again, it is not clear whether these variables have a direct effect on treatment response or a more indirect effect through relationships with other moderators such as motivation for treatment, compliance, and so on.

4. *Severity of cocaine dependence.* Emerging evidence points to severity as an important prognostic indicator in general (Carroll et al.

1993*b*; McLellan et al. 1994), as well as a treatment-matching variable (Carroll et al. 1994*a*). As there is likely to be high correlations between severity and other prognostic variables such as sociopathy, family history, severity of psychosocial problems, age of onset, and so on, a more parsimonious strategy for evaluating this set of variables may be through multidimensional subtyping, a promising strategy developed in the alcohol field (Babor et al. 1992), which has been recently shown to generalize to cocaine abusers (Ball et al. 1995).

5. *Route of administration.* Nunes (this volume) reports data linking route of administration to antidepressant response, with better outcome for intranasal users than freebase/crack users. Again, route of administration may function as a proxy for a number of indicators, such as severity and chronicity of drug use, SES, and polysubstance use.

6. *Primary drug and treatment setting.* Findings based on individuals whose principal drug dependence diagnosis is cocaine may not generalize to samples composed of methadone-maintained opiate addicts who have developed secondary cocaine dependence, and vice versa, because of large differences in patterns and levels of psychopathology between opioid and cocaine populations (Rounsaville et al. 1991), reinforcement contingencies in the two treatment settings, and so on.

7. *Comorbid alcohol and other drug use.* Alcohol dependence frequently co-occurs with cocaine dependence (Regier et al. 1990) and has been associated with poorer prognosis (Carroll et al. 1993*b*). Several distinctive features of this subpopulation suggest specialized treatment strategies may be needed (Carroll et al. 1993*c*; Higgins et al. 1991).

8. *Comorbid psychopathology.* As noted earlier, differences in rates of comorbid disorders across studies are likely to produce differences in medication effects, particularly for psychotropic agents where effects may be mediated by the presence of psychopathology. At a minimum, any study sample should be described in terms of rates of current and lifetime DSM-IV disorders, particularly affective, anxiety, and antisocial personality disorder. Global ratings of psychopathology, such as the psychological section of the Addiction Severity Index (ASI), should also be included, as should continuous

ratings of specific psychological symptoms, including depression and anxiety. The recent reports regarding the significance of sociopathy as a moderating variable for medication response (Arndt et al. 1994) also suggests that categorical (e.g., DSM-IV diagnosis) and continuous ratings of sociopathy, such as the California Psychological Inventory-So (Cooney et al. 1990; Megargee 1972) should also be included.

9. *Motivation and contingencies.* An individual's motivation for treatment and level of readiness to change may be an important determinant of treatment compliance and response (Prochaska et al. 1992). For example, Hall and colleagues (1991) found cocaine abusers' commitment to abstinence significantly associated with the likelihood of relapse. This important dimension has been infrequently assessed in clinical trials evaluating pharmacologic treatments for substance use disorders and may be helpful in identifying those individuals who are not likely to benefit from treatment in a given trial (Moras 1993). Similarly, the source of the individuals' treatment referral and powerful contingencies associated with some referral sources (e.g., employee assistance program, court system, child welfare) may play a role in their motivation for treatment and should be assessed and described.

## SUMMARY

The two examples provided in this chapter suggest that the inconsistent findings across studies evaluating identical pharmacologic agents may be associated with variations in sample characteristics, particularly those associated with (a) general treatment responsiveness (e.g., severity of cocaine use, sociopathy), or (b) responsiveness to specific treatment strategies (e.g., rates of depression where antidepressant agents are evaluated). Describing study samples and evaluating treatment response along multiple dimensions, using a common set of standardized assessments, would be an important advance in understanding variation in subjects' response to medication effects and comparison of findings across different studies. Moreover, consistent description of study samples across a number of dimensions would set the stage for meta-analyses of patient-treatment interactions. Similarly, as new medications are developed and evaluated, variables that have a theoretical basis as mediators of treatment response should be identified and evaluated. It should be noted, however, that success profiling and matching research is more complex than the search for simple main effects (Finney and Moos 1986; Project MATCH Research Group 1993). In particular, adequate power to detect patient-treatment interactions requires much larger sample sizes than those that have to date characterized pharmacotherapy research for cocaine dependence. This strategy, however, is likely to enhance the development of effective pharmacological interventions for this very challenging patient population as researchers' understand the complex processes associated with treatment seeking, retention, and outcome among cocaine abusers.

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# Baseline Assessment, Study Entry, and Stabilization: Double-Blind Clinical Trials in Drug Dependence

*John Grabowski, Gila Arnoni, Ronith Elk, Howard Rhoades, and Joy Schmitz*

## INTRODUCTION

The conduct of clinical trials in psychopharmacology, including the area of drug dependence, has special complexity because the disorders reflect the interplay of pharmacological, biological, behavioral, and environmental determinants. Many issues concerning clinical trials in psychopharmacology have been addressed by Prien and Robinson (1994). The study of new medications for the treatment of drug dependence has presented challenges (Blaine et al. 1994). In the case of cocaine dependence, these have included difficulty in recruiting uncomplicated patients (i.e., those who do not have multiple medical, psychiatric, or severe additional drug dependence problems), and high dropout rates. Many of the problems are not unique to drug-dependent patients generally, or cocaine-dependent patients specifically, although they are still described in these terms (Blaine et al. 1994). Rather, there are commonalties in problems, research issues, and probably treatment elements across disorders that are heavily imbued with both behavioral and biological components. This is particularly true with respect to issues of "compliance" or adherence to treatment. O'Brien and McLellan (1996) reported that observed rates of noncompliance with medication regimens and other features of treatment are equally common with disorders such as diabetes and heart disease, as they are in substance abuse. Clearly, differences among habitual behaviors (Levison et al. 1983), and medical disorders where problems of compliance are common, cannot be ignored, but the drug-dependent population is not unique with respect to adherence to treatment regimens. At least some of the issues can be resolved by precision in defining the design and mechanics of each clinical research study. Some clinic-specific efforts have been described previously (Elk et al. 1993).

Conducting definitive scientific studies of medications becomes more difficult in the face of noncompliance or multiple disorders. Yet many of these difficulties can be confronted and resolved in planning systems for the conduct of the research (Kartzinel et al. 1994). Particularly important are the initial contact, intake, and period of stabilization before study entry. Overeagerness to conduct the clinical trial may produce simple procedural errors that negate the studies value. This can result in failure to demonstrate efficacy where it exists, or perhaps more damaging, produce reports of efficacy in the absence of actual benefit.

It is assumed at the outset that there is little value in nonblinded trials lacking placebo controls. Indeed, as Kupfer and colleagues (1994) have noted, "it can take years to overcome the results of flawed trials," and at least some of the research in this field has been devoted to that task. Thus, this chapter is pro forma and the information should be familiar. Nonetheless, investigators may benefit from rethinking standards, biases, preferences, and idiosyncrasies of the field. The goal is to describe some mechanical steps contributing to effective baseline assessment and study entry. Precision at this stage is critical insofar as subsequent measurements hinge on the validity of initial contact, intake, and stabilization. The procedures and issues considered here are drawn from experience and problems evident in the current literature. Strategies described have been used successfully over the years at the Substance Abuse-Medications Development Research Center (SARC), at the University of Texas. Some theoretical and practical issues in clinical trials that might influence the generalizability of study results are also discussed.

## BASELINE ASSESSMENT

### Standardization

Underlying the data collection process is the need for standardization of recruitment, baseline assessment, and stabilization. Standardization is critical if replicable and generalizable results are to be obtained from clinical trials evaluating new medications for the treatment of drug dependence. At the level of mechanics, important factors may be overlooked by novice and experienced investigators alike.

## The SARC Clinic

The SARC Clinic was developed under National Institute on Drug Abuse (NIDA) demonstration grant DA 06143 as a new research treatment facility in 1989 and has no nonresearch service component. The focus was on new treatments for drug dependence and reduction in HIV transmission. There existed the opportunity to explore optimal procedures (Elk et al. 1993), although there is continuing refinement. A major issue in developing the clinic was to avoid pitfalls including eliminating or minimizing common deterrents to patients seeking treatment or deflecting them from research participation. Many of these problems emerged during the initial contact and stabilization. There is benefit in detecting misassignments or other problems early, thereby increasing efficiency of the process.

An important feature in the development of the clinic was that it should be comfortable and provide readily accessible service to drug-dependent patients with little risk. It seemed likely that this would maximize the baseline level of retention with respect to obvious resolvable problems. The physical environment is well maintained and is a standard reasonably appointed outpatient clinical care facility resembling that of other specialty clinics. A variety of provisions to assure comfort, safety, and efficiency of service were also established, while at the same time maximizing collection and accuracy of data for clinical trials. Those devoted to assuring the safety and comfort of staff and subjects/patients are listed in table 1 (also see Grabowski et al. 1993).

The description derives from approximately 25 projects implemented between 1988 and 1994. These have involved about 1,000 enrolled patients and many more initial contacts and screens, in studies of opiate, cocaine, nicotine, benzodiazepines, and other forms of drug dependence. The studies, which included a range of special populations as well as "uncomplicated" patient population, included about 31,000 urine screens, 67,000 doses of medication, and multiple administrations per patient of Profile of Mood States (POMS), Addiction Severity Index (ASI), and other instruments to each patient.

## Patient Recruitment and Advertising

Advertising is a common means to obtain subjects for clinical trials; each successive advertisement increases the number of telephone calls. Although not yet thoroughly documented, there appear to be differences

**TABLE 1.** *Examples of fixed clinic-wide contingencies and the nature of consequences for patients.*

1. Regular attendance for continued treatment +/-
2. Maintain appointment time for counseling +/-
3. Maintain appointment time for medication +/-
4. Complete data and information update forms +/-
5. Return medication bottles +/-
6. Provide urine samples for drug screens as scheduled +/-
7. Arrive and depart in reasonable time (no loitering) -
8. Maintain clean air (no smoking) -
9. Contribute to a physically healthy clinic (no weapons) -
10. Support the clinic as the sole vendor (no drug dealing) -
11. Responsiveness to chemistry laboratory findings (no arguing)

NOTE: This table lists issues/behaviors that underlie problems in some drug dependence treatment clinics. Focus on these issues often interferes with service delivery. Generic provisions can be added or eliminated as needed. Positive (+) and negative (-) consequences must be clearly stated and systematically applied. The goal is specification of positive consequences where the absence of that consequence is itself unpleasant. Items 9 and 10 have attached consequences of warnings and potential discharge. Some issues such as discussion of accuracy of laboratory drug screen results have neither positive nor negative consequences; they are not open for discussion just as blood pressure readings are medical test results accepted without discussion.

in the populations as a function of advertising site, even within the same newspaper (e.g., front news section, sports, entertainment sections). These differences also prevail as a function of contacts with emergency rooms, psychiatric facilities, and the extent to which current patients refer new patients. This affects the rate of acceptable patients for any particular study.

## Screening

Sites that advertise for subject patients must screen call-in and walk-in candidates alike. The proportion of acceptable subjects depends in part on the specificity of the advertisements. Some individuals call because they have learned from friends, or from other treatment sites, that treatment research opportunities are available. Since treatment research sites often pay for initial interviews and other time devoted to research, it can be expected that some individuals call for the opportunity to earn money. The number of false-positives invited for a full-intake screening appointment depends in part on the adequacy of the prescreening interview whether administered by telephone or in person (table 2).

Two problematic features emerge in recruitment at this level. One is that different information accrues to subjects depending on the source (advertisements, professionals, friends). Second, there is a tendency to treat potential subjects who walk in differently from those who make initial contact by telephone. Using the “bird in the hand” philosophy, an investigator’s eagerness to enroll subjects may lead to special provisions being made for subjects who are already at the site. The inherent bias in these differences dictate that all subjects should have the same initial screening interview, whether by telephone or in person. Until it can be demonstrated that there are no differences between the patient who takes the time and trouble to attend the clinic for initial screening and those who call in, differences should be assumed.

Each deviation risks additional variability. Following this constant first contact, the same procedures are applied to patients regardless of source of entry. There is no difference between subjects in scheduling of appointment; for example, candidates who call, are referred, or walk in are scheduled in the first available intake session. No preferential provisions are used in this regard.

The use of the prescreening form also permits the researcher to obtain rudimentary data on the characteristics of individuals from the community who are seeking treatment. This provides additional information for a cumulative database on the status of treatment research seekers in the community.

Some special prescreening provisions should exist when there are multiple investigators with multiple studies at a site. The “big primate” principle may prevail in assignment, with the most senior investigator

**TABLE 2.** *Prescreening (telephone or walk-in) questionnaire.*

A. Introduction

1. *Treatment Research Clinic, this is (your name). May I help you?* Determine why individual is calling. If not immediately obvious from response, ask:
   —*Are you calling about an advertisement?* (If so, which ad?)
   —*Are you calling about receiving treatment?* (If so, what program?)

2. Preamble
   *We have several different research programs available to provide different treatment for different drug or medication-related problems.*
   *I must ask you some questions to learn if you qualify for these and to decide which one might be best for you.*
   *Before I do, I want you to know that all of the information you give me will be strictly confidential.*
   *I will not ask for your name or telephone until we complete the interview so that you can feel free to answer without any problems if you decide not to continue. If you decide to make an appointment, I get the necessary information. I will now ask the questions—may I start?*

B. Determination of Study Type

1. *For what type of drug or medication-related problem are you seeking treatment?* (circle 1): None, Cocaine, Opiates, Anti-anxiety medications, nicotine, other______________
   If cocaine:
   a. *Are you currently having a problem with depression?* (Elaborate) Yes No
   b. If yes: *Do you think your depression is only a result of your cocaine use or does it seem to be a separate problem?* If response = separate, refer to Cocaine+Depression Project.

2. Circle: Male Female

3. If female: *Are you pregnant?* Yes No
(Use flowsheet to determine procedure for pregnancy study.)

**TABLE 2.** *Prescreening (telephone or walk-in) questionnaire (continued).*

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4. *Have you have a positive TB skin test?* Yes No
    a. *If yes: Have you had treatment for it?* Yes No
    b. *If yes: How long was the treatment?* ________

C. Standard Questions (all studies)

1. *How did you hear about us?* ______________________________

2. *How long have you been using this drug?* ____________________

3. *Have you had any therapy for your drug use in the past 6 months?* _____________

4. *What is your ethnic background? a. Caucasian, b. Black, c. Hispanic, d. Asian, e. Other*

5. *How old are you?* _______________

6. *What is your Zip code?* ___________

D. GO TO APPROPRIATE STUDY-SPECIFIC QUESTIONNAIRE.

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NOTE: All potential subjects are queried with the above form. If they qualify at this level, the next set of questions concerns a specific study that is appropriate for the presenting condition. The entire prescreening process takes about 15 minutes. An appointment is made for an intake interview scheduled within 24-48 hours.

having first access to subjects for his or her studies, and this may be a source of bias. A site should have a systematic means to rotate through candidates if multiple studies with similar criteria are ongoing. The screening procedure for inclusion and exclusion then becomes stepped, as follows.

1. Summary demographic information and statement of problem.

2. Designation for screening for a particular study or rotation for a class of studies.

3. Screening to determine appropriateness before making intake appointment.

4. Return to the general screening pool if the potential subject is found to be ineligible for the study for which he/she was first screened.

The extent to which preferential recruitment for one or another study introduces bias is unknown. However, it is intuitively sound to avoid the possibility of assignment bias whenever possible.

## INTAKE

The intake procedures in all studies should be pedestrian but rigorous, systematic, and unbiased, protective of subjects rights, and informative of subjects' responsibilities. Failure in this domain can produce high dropout rates and produce results that cannot be replicated.

### Consent Procedures

Sites differ in the characteristics of the consent procedures since variation within the broad National Institutes of Health (NIH) guidelines is permissible under the arrangement of local Initial Review Boards (IRBs). Requirements vary for style and other features of advertisements, consent forms, and supplementary information, despite the common required elements of consent procedures. The likelihood of this having an effect on recruitment, screening, and intake procedures is unknown.

Variation in initial intake may occur at a site due to differences across intake personnel and most certainly occur across sites. Sources of within-site differences may be due to different approaches to candidates based on biases involving perceived differences among patients. Thus, potential subjects may receive more or less information depending on unspecified ad libitum criteria imposed by the intake staff members (e.g., perceptions of intelligence, affluence, etc.). Thorough, well-documented consent forms, intake procedures, regular training and retraining, and relatively inflexible interviewing guidelines should minimize these problems. Further, monitoring for consistency within and across staff members should occur. This can be accomplished through regular audiotaping of consent, intake, and other sessions. Regular meetings of intake and diagnostic staff members may help preclude drift in adherence to the criteria applied during the course of a study.

Since local IRB criteria may produce differences in length or other characteristics of consent forms, greater consistency can be achieved by having supplemental descriptive material, though this too must be submitted to the IRB. The material may be a useful additional guide to a patient after he or she has departed the premises. It should include information about fixed appointment days, times, and detail regarding provisions for continued participation as well as reimbursement. Here, as in other procedures, the goal is to reduce unnecessary variability in the experiences of subjects/patients entering a study.

When the agreement to participate has been obtained, the evaluative intake process is another source in which variability may arise. Consistency of measurement and application of diagnostic criteria is essential.

## Diagnoses

Specific instruments used in diagnoses have been discussed at length elsewhere in other volumes in the NIDA Research Monograph Series. However, two points should be made. First, recall that many instruments were standardized on populations that may be rather different from the drug-dependent population. Further, some, such as the ASI, were developed using populations that may or may not be representative of the broader treatment-seeking population. Second, from the point of view of research and data analysis there should be an effort to minimize the number of instruments. This quest resides in the simple problem that increasing the number of measures and items increases the opportunity for statistically significant but spurious and clinically irrelevant findings. Assuming that appropriate instruments are being used, the critical issue is that inclusion or exclusion relies on the standardized criteria. The authors' intake procedures included:

A. Prescreening for general acceptability for study as described above.

B. Intake screen.

    1. Complete medical evaluation including HIV, TB, EKG, drug screens, and other standard tests.

2. Complete psychiatric/behavioral evaluation including SCID, ASI, POMS, Hamilton A/D, and detailed drug history.

3. HIV testing/counseling-HIV risk behaviors.

4. Self-report instruments: POMS, Beck, desire to use drugs (craving).

If at any point during the intake process a potential subject is to be excluded from his or her assignment, there are two possible outcomes. First, the individual may be appropriate for evaluation for another ongoing study. At this point the intake continues, including any special items appropriate to the new assignment. If the subject cannot be included in any of the available studies, he or she has the opportunity to meet with a therapist to arrange for referral to other treatment sites.

A special problem emerges in the domain of substance use disorders. Oddly, because of the imprecise use of language, implementation of studies sometimes falls victim to words such as “abuse” when “dependence” is intended, and vice versa. Precision in terms of daily discussion among staff members should be encouraged since it reduces confusion and contributes to the integrity of the subject intake and baseline assessment procedures. Beyond this there is the lay vernacular, which permeates the field. In its 1994 publication guidelines, NIDA explicitly noted that terms with pejorative baggage, such as “addict,” should be avoided, and this applies as well to the extant clinic and staff meeting vocabularies. There are no parallels evident in other domains of medicine or psychology, yet the problem of applying nontechnical terms to drug-dependent patients is common in the professional community. Care in language may also contribute to better educating the subject about the disorder and thus real benefit can accrue to the patient as a research subject. Prior to each study, all intake staff members and clinicians as a group must review the conditions and criteria for entry again with a view to assuring that there is familiarity with the study-specific procedures (i.e., that they are implementing the same study).

Further, the authors have found it useful to be exclusive in screening with respect to diagnosis, preferring to err on the side of not including subjects for whom the diagnosis is less clear. Inclusion of dual-diagnosis patients can occur and have obvious undesirable consequences in a study intended to focus on one disorder, e.g., cocaine dependence. An extremely heterogeneous patient population with a variety of secondary disorders, e.g., depression, antisocial personality disorder, and no ability or intent to stratify, may produce substantial variability. Clearly, this may be particularly problematic in an early efficacy trial, though it may be more acceptable in effectiveness studies, which typically account for this using a variety of procedures including larger sample sizes. As a matter of comparison to other areas, inclusion criteria in studies of antihypertensive medications, dermatological preparations, or other medications for medical conditions, tend to be characterized by considerably less variability for confounding conditions than is often found in studies of medications for drug dependence. Though it is often argued that users of single substances are rare, the authors have found persistence in recruitment can result in an adequate sample of subjects meeting the specified requirements and intent of the study without compromising the inclusion/exclusion criteria.

Heterogeneity of patient populations and differences across sites may have contributed to the equivocal results reported in the literature for some medications for drug dependence. For example, some studies reported modest or great improvement and still others report no change with desipramine (Arndt et al. 1992; Gawin and Kleber 1984; Gawin et al. 1989). Similar uncertainty has arisen in the case of fluoxetine (Batki et al. 1993; Grabowski et al. 1995). Characteristically excluding patients who have additional diagnoses (depression, antisocial personality disorder) or secondary conditions (AIDS) other than the specific drug dependence of interest may contribute to definitive findings in both efficacy and effectiveness trials (Grabowski et al. 1995). Arguably, costs are increased at the front end of a study due additional screening to achieve the desired sample. Nonetheless, it appears worthwhile to reduce variability to permit focus on the key issue; i.e., does medication X, under setting conditions A and B, and behavior therapy conditions C and D, produce benefit, no effect, or harm. Unambiguous criteria must be determined and applied during the initial screening, intake, and stabilization phases, and continuity must be sustained, often over a period of many months or several years.

## Urine Drug Screens

Drug screens provide a critical element in defining the characteristics of the patient population at entry and during stabilization. Clinical and research staff must emphasize the importance of these data and the need for care in collection, transport, testing, and reporting (Hawks and Chiang 1987). Having a professionally constituted analytical chemistry laboratory on site provides greater assurance of reliability. Equally important for behaviorally based studies is that an onsite facility provides for immediate results when called for by contingency management procedures. Not all sites can afford or require this level of participation by chemists and other technical personnel on site. Offsite laboratories providing slower turnaround times may be satisfactory during ongoing standard medication clinical trials. However, this necessarily slows the process of study entry, while awaiting the results of intake and stabilization drug screens. Slowing the intake process may in turn lead to failure of patients to return and slow overall study progress.

There is ongoing discussion of the type of screen required: qualitative, semiquantitative, or quantitative. In standard clinical trials semiquantitative urine screens should be sufficient and even qualitative results may suffice. Arguments for quantitative screens have emerged, but the supporting data for this position are not entirely persuasive. One concern is that qualitative or even semiquantitative screens must be interpreted in terms of cutoffs (e.g., 350 ng/mL). This was an arbitrary determination originally standardized for workplace screening where no use was acceptable and a minimal allowance for error was permitted. It is argued that a medication may reduce the level of dependence or abuse, but that this may go undetected unless quantitative screens are used. It could be argued that an effective medication (such as paralleling methadone in efficacy), would produce group reductions from 100 percent positive to 10 to 20 percent positive screens even by this stringent criteria. An alternative position is that a higher cutoff point could be used that would itself indicate relatively low levels of drug use. For example, since cocaine-dependent or -abusing patients often have benzoylecognine levels between 100,000 and 1 million ng/mL, a cutoff of 5,000 to 10,000 ng/mL would reflect significant change for most groups of patients.

The perspectives represented in the ongoing debate reflect conceptual as well as practical shifts in thought. There is increasing recognition that both risk reduction and risk elimination are important, with the former being satisfactory when the latter cannot be achieved. Whether strict elimination or risk reduction views are held, definitive and consistent criteria and effective procedures must be established and maintained at intake and stabilization as well as throughout the study. Drift in procedures can occur over the course of clinical trials that may take several years to complete. Permitting consistent comparison of data over time and within and across subjects must be avoided.

Other problems emerge with respect to medication-taking behavior and drug screens. To accommodate this, it may be useful and cost effective to differentiate phases of evaluation with respect to the comprehensiveness of screens. Given a relatively high level of tricyclic antidepressant use in the community of cocaine-dependent patients (approximately 8 percent) the authors screened for both drugs of abuse and a full range of therapeutic medications in the initial screens. Reviewing this process, it was determined that an acceptable level of safety and rigor can be achieved by conducting comprehensive semiquantitative drug screens for common psychiatric medications at intake and monthly thereafter, while the twice-weekly (or more frequent) screens during study are restricted to commonly abused drugs.

In discussing the quantitative-qualitative issue, it may be necessary in early trials or certain types of combined medication behavioral therapy trials to obtain quantitative screens. However, semiquantitative screens should be adequate. The adequacy of this approach is testable. The authors' approach is that in a new series of studies quantitative screens are conducted for all drugs on all patients, and then varying cutoffs and criteria and results with respect to clinical utility are compared and applied. Future screening procedures will depend on the outcome of this comparison. Periodic blood screens may be useful for determining medication levels. At the same time, several studies in the literature, including the authors' work with fluoxetine, suggest little relationship between clinical effect and blood levels of commonly examined therapeutic medications. Clearly, when examining new medications, this issue must be evaluated.

## Medical Evaluation

The medical evaluation while standard requires special attention to preclude unnecessary exclusion of potential subjects. Patients should generally be in good health except for problems directly related to drug use. Problems at intake may include results indicating aberrant EKG or liver dysfunction, placing a patient in a position of being borderline acceptable for a study. However, if the patient is otherwise acceptable, monitoring during the stabilization period will either mitigate concerns as symptoms abate or lead to exclusion. Dubious results that indicate greater than average risk as specified by the IRB human subjects provision require special attention. Thus, it may be necessary for a specialist, e.g., a cardiologist, to review a record before the patient may actually receive the study medication. Unlike many of the compliance issues, this matter is of greater concern with drug-dependent patients since they may take additional drugs while receiving the therapeutic agent. Even with an effective medication it can be expected that this will be particularly likely early in treatment, thereby increasing risk and potential harm. It is during baseline assessment that these issues must be addressed. Thus, in the authors' studies of stimulant replacement, EKGs were conducted three times weekly in the first 2 weeks and once weekly thereafter. Sites unprepared, or unable to provide this level of evaluation, should be still more cautious in these initial evaluations.

## Behavioral and Social Evaluation

Behavioral and social status/function evaluations are typically viewed as essential during the course of the baseline assessment. Data pertaining to these domains can be derived from standard diagnostic instruments, notably the ASI and SCID interviews. There appears to be increasing evidence that most demographic measures (e.g., race, income) have little relevance in examination of correlations with treatment outcome. Rather, factors proximate to drug use (e.g., drug, dose, severity, route), as well as comorbid psychiatric conditions may be most important. Certainly, a comprehensive drug history, particularly with respect to recent patterns of use, can be important and can be linked to the drug screen data. Further, the behavioral features of drug taking serve as the best dependent and independent variables. Of less clear value are measures such as dollars spent, grams used, and so on, unless they can be documented and validated against status of drug supplies in the community, (e.g., through the DEA). Drug prices and quality vary tremendously from time to time and across sources at the same time, thus diminishing even the face validity of such measures. While often reported, the generalizability or utility of such surrogate measures of drug use has yet to be demonstrated.

Useful data can be collected using queries focusing on patterns and circumstances of drug use. The Drug Use Desire Inventory, which relies extensively on operational definitions of behaviors thought to reflect craving, is used in the SARC Clinic. The principal problem with such measures is establishing definitive linkage to actual drug use. Particularly problematic, though conceptually interesting, is the not uncommon result of divergence of drug taking and self-report measures of desire to use as has been reported by Fischman and colleagues (1990), with desipramine.

## Summary

The process of assuring quality and consistency in these phases of research is iterative and developmental; each member of the group contributes to inservice training on components of the process. Effectively, a checklist is developed assuring that all components are in place and agreed to before studies commence. The screening and intake process should be viewed as mechanical, with little room for error, producing data on which success of the results hinge. Each individual involved in the process can inadvertently tinker and contribute variability. Many baseline assessment data can be directly entered into a computerized database, while others must be entered by hand at the earliest possible time. All files, papers, and computers should be sampled for accuracy. Further, all files must be retained to permit retrospective checks as needed. The authors have developed a computerized network system with terminals at the pharmacy medication-dispensing window, in intake interview offices, with research assistants, and in data coordinators' offices, to provide for regular patient checks and data entry. Messages to patients flow easily between clients and staff they have contact with to assure intake elements are completed and medicating sequences are initiated. Making a brief summary of the intake procedures produces an interactive process that permits improvements and minimizes errors. Beyond this a clinic operations manual should be available for all new staff members and should be reviewed periodically by all staff members to keep the manual procedures current.

## STABILIZATION AND STUDY ENTRY

### 2 Weeks of Stabilization

Patients accepted for studies undergo a stabilization period prior to study entry. The scientific and practical advantages and disadvantages are discussed below.

As outlined earlier, there is concerted effort to assure that all patients receive the same information, agree to the same requirements of participation, and receive similar treatment at entry. Beyond this, however, there is a need to verify that the initial determinations are accurate. Acutely, it is to the investigator's disadvantage to need to reexamine since it is costly and may result in discharge of subjects; in the longer term it assures the validity of the sample and the results of costly and time-consuming clinical trials.

## Evaluations During Stabilization

Patients should be monitored closely for a period of 10 to 14 days after intake. Study requirements and complexity of expected problems may result in clinic attendance from 2 to 7 days per week. Drug use may likewise be monitored through two to seven scheduled urine screens per week. Immediate return of urine screen results (within an hour) may be necessary in some cases, but return by the next visit is essential. Medication doses should be increased systematically during this period and the consequences of dosing observed; this will vary across medications. For fluoxetine, ritanserin, risperidone, and methylphenidate studies, the authors considered it appropriate to obtain additional EKGs, while in methadone studies this requirement was not included.

Patients must be monitored to determine whether conditions apparent at entry such as depression wane during this period, and to determine whether previously unobserved symptoms emerge. It has been noted in the literature (e.g., Blaine et al. 1994; Kadden et al. 1995) that psychiatric diagnoses should be reassessed to determine whether an observed condition was stable or an artifact immediately preceding drug use. Ostensible coexisting depression is commonly noted in individuals who have recently ceased using cocaine, but in 60 percent or more of the cases, reevaluation demonstrates that the dual diagnosis disappears within 2 weeks. While demographic factors seem to have little bearing on outcome, comorbid psychiatric conditions or their absence does seem to be important with respect to treatment outcome, and thus with respect to the conduct and results of the clinical trial.

Finally, a fixed series of general queries should be posed at each session during this period concerning changes in legal status, living conditions, and social status in terms of significant others. These can warn of potential problems, assure that the patient continues to meet study criteria, and can also be checked against intake data derived from measures such as the ASI. Assuring that the subject clearly understands the requirements of the study can be accomplished by through repetition during the stabilization period through formal and informal means. It may be necessary to revisit consent procedures if it becomes apparent that the patient was not intact during the initial study introduction (Grabowski et al. 1979).

Therapists, research assistants, nurses, and any other staff members having contact with subjects can establish the framework for patients' participation during the stabilization period, making certain that fixed appointment conditions are met, that urine screens are delivered, and that materials are completed. Patients can be given a printed description that includes their regularly scheduled appointment time, other scheduled events such as urine screens, and delineation of items for which they receive research payments. These efforts promote a baseline level of compliance on which medications and behavioral therapy combinations can be evaluated. These constructive procedures are standard of care in some clinical settings but are rarely used in drug dependence research, where compliance is essential to rigorous evaluation.

## Other Factors Confounding Assessment and Treatment Studies

Disregarding a long list of minor factors that may confound baseline assessment specifically and treatment research projects generally, there remain examples of major issues that may dramatically affect results. An illustrative example is provided here that is typically ignored, accepted with resignation, or encouraged and defended by many in the field of drug dependence. This is the issue of patient/subject attendance of self-help groups in the community and outside the control and purview of the study.

The baseline assessment is an important opportunity to determine whether other factors may confound the basic study of medication (or behavioral) therapy efficacy. The problem with self-help groups is clear. When evaluating a medication for hypertension, diet modification, exercise behavior, or seeking other treatments during the course of the study would be discouraged. Thus, researchers are particularly attentive to the issue of alternative ongoing therapies of any form for several reasons. Baseline data collection will be distorted in unknown ways by these activities. Beyond this, encouraging or not dissuading patients from extracurricular treatment activities assures a source of confound of unknown dimensions. During the stabilization period, researchers consistently emphasize the importance of adherence to the current therapeutic program. It is clear that the other activities may or may not be helpful but that the subject has agreed to participate in a specified treatment regimen for a defined period. In brief, researchers are committed to providing a particular range of treatment and committed to complying with this regimen. A variety of strategies are used. Remarkably, investigators conducting evaluations of medications for drug dependence both fail to discourage and may encourage attendance at self-help groups. Arguably, patients can seek to deceive the investigator. The authors view the effort at educating and obtaining compliance on this issue critical. Other sites prefer to account for this in other ways but only infrequently report the data. This single factor may contribute substantially to some problems observed in the literature. So-called self-help groups can have positive or negative effects and vary widely in focus, format, and extent to which they alter behavior. Often the message conveyed therein is directly contradictory to some cognitive behavioral strategies. The authors feel strongly that there is a need to assure that the treatment being evaluated is to the extent possible is the one being delivered at the study site. Again, by analogy, if patients in the hypertension study or a psychotherapy study were receiving prescription medications elsewhere or were self-medicating with active OTC medications, it would be cause for exclusion. The same should apply to supplemental doses of self-help groups. Other sources of variability are much more widely recognized and accounted for and will not be addressed here. The example of self-help groups is emblematic of some of the problematic issues that confront the field and must be considered in the baseline assessment phase.

Another problem is that of accepting intent to treat as an essential criterion. At the extreme, it proposes that every subject who enters the clinic and signs a consent form must be included in subsequent analyses since there was a so-called intent to treat. The question is: Intent to treat what? Should misdiagnosed individuals be included? For example, in a study of depression+cocaine dependence should subjects be included whose depression lifts after several days? Or should patients who do not tolerate a dose of a widely used medication be considered as failures? The liabilities of this strategy are considerable. An obvious potential problem will come from rejecting medication or behavioral therapies that are effective.

Other problems common to the study of drug dependence treatment research, baseline evaluations, and design result from common myths or untested assumptions that are woven into the fabric of clinical trials. The problem of self-help groups has been mentioned; the view that patients must hit bottom is sacrosanct only in drug dependence and would be anathema in any other domain of medicine; the views regarding optimal setting conditions (e.g., inpatient, long duration therapy); that drug dependence is not fundamentally a real biological/psychological disorder: all contribute to confounds in efforts to develop optimal treatments.

While there is an increasing body of literature contesting these beliefs, they present continuing challenges in the objective study of substance use disorders. These are apparent problems to the extent that these views permeate the views of staff members conducting the intake process.

### Study Entry

The subject who completes the 2-week stabilization period with a stable diagnosis, with all other medical and psychiatric criteria met, and accepting all other conditions of study inclusion enters study and is not replaced. The importance of this continuing assessment period is exemplified in studies whether fixed or variable dosing prevails. The issue is particularly important in the former case such as the authors' fluoxetine study involving a placebo, 20 mg, and 40 mg of medication (Grabowski et al. 1995). If subjects were considered entered to a study before it is was determined that they can tolerate the assigned dose, differential dropout may skew the results. The same problem applies to other factors as well. For example, patients may state that they can attend a clinic 2 or 5 days per week but differential attrition may prevail for working patients assigned to the condition, requiring more frequent visits. Again the results will be skewed. Many patients enter a study with liver function values that are borderline; the stabilization period permits determination of whether the values are stable, improving, or deteriorating (thus making the subject unacceptable for inclusion). In sum, the stabilization period permits evaluation of the practicability of study conditions for a particular patient while also providing for monitoring of the validity of the initial intake assessment.

When the subject is considered an active study participant a standard metric is applied to continued participation. The subject must sustain a level of 75 percent of his or her study commitments (e.g., urine screens, self-report form sessions, medication visits, therapy appointments). The actual percentage is arbitrary and should be established for the study and be somewhat flexible. In practice, the main function of this criterion is to provide a definitive endpoint for patients who drop out.

### Problems

There are obvious problems with the stabilization strategy. For example, in the normal course of events, many subjects/patients leave treatment shortly after entry or within the first 2 weeks. Thus, apparent retention may be inflated if patients are not considered subjects until they have stabilized. This can be accommodated in the data-analytic process and description where the progression of attrition should be noted. For example, the number of individuals who underwent initial prescreening can be specified: those who entered intake but dropped out or were excluded and those who dropped out during stabilization. Data should be maintained for all patients and examined for differences among and between individuals who departed during stabilization and those who remained to become active subjects. Again, in a large study of fluoxetine, this procedure was found to be effective and there were no significant differences on the measures used between patients who departed during stabilization and those who were retained. Another obvious problem resides in added cost; however, it should be apparent that careful screening, albeit costly, is ultimately one of the most cost-effective features of the study process.

## Summary

Despite the seeming complexity of the procedures described, they have proven generally acceptable in the authors' studies. Much of the mechanical character of the process is transparent to the patient. Precision is requisite for the difficult area of study comprised of clinical trials to determine the efficacy of medications for drug dependence. There are considerations in medications development clinical trials that are overlooked. These include reevaluation postentry; prestudy to permit replicable comparison throughout the study, and finally assuring that the treatment being evaluated is the only one that the patient is receiving.

In the fluoxetine trial used as an example to this point, approximately 500 patients called (or walked in) and were thus screened using the telephone screening form. Most screened out at this level were polydrug users or had legal charges pending that might have interfered with participation. About 228 went through the intake procedure. Ultimately, 156 were completed stabilization and were formally considered having started study. The stringent requirements described to this point were applied. The end result was an uncompromised double-blind trial (Grabowski et al. 1995). Randomization has been successful in all of the authors' studies to date using these procedures. It is possible that consistently similar results could be obtained with less rigorous procedures; however, less rigorous or inconsistent intake procedures may well contribute to equivocal results in the literature.

## OPTIMAL DESIGNS

Comment on design issues is warranted here at two levels, in addition to those by Nunes (this volume). First, it appears that despite flaws, the stabilization period as a formal study component is essential in this population, at the current level of understanding of the conduct of medications development trials. As noted earlier, this is particularly important to assure that all patients identified as such received the full dose. This was and is critical to evaluation of clinical efficacy and effectiveness.

Beyond this, it is suggested that variations in experimental designs should enhance detection of benefit, lack of change, or harm in medication trials. Medication trials for drug dependence are confronted with the issue of complexity of the disorder. Elaborate behavioral treatments as a baseline could conceivably obliterate differences between groups attributable to medications. Yet it is recognized that joint actions between behavioral therapies and medication may enhance effectiveness. These can be approached as two distinct types of studies. They may at times be examined concurrently, in the following manner: An extended (e.g., 6-week) double-blind baseline period with placebo and medication using standard care (e.g., one therapy session per week) could provide a rigorous test of the medication. Substantive reinforcers could be provided for retention but not contingent on reductions in drug use. If an effect is observed under the austere standard condition, the medication might be viewed as an important candidate for further examination. During such a period, a medication such as methadone would readily be determined to reduce opiate use. If no difference was observed during this period, the medication might be sacrificed as a candidate. If pronounced or even modest differences are observed, application of intensive behavioral interventions could be applied to half of the initial remaining subjects in each group. This would permit evaluation of the extent to which a behavior therapy medication interaction produces further change. Disproportions in group size could emerge in the second phase of this design if the medication was effective. However, this design or some other hybrid could greatly reduce the cost, time, and steps involved in initial trials of efficacy and effectiveness.

## OPTIMAL DATA-ANALYTIC STRATEGIES

The authors are currently examining optimal data-analytic strategies permitting capture of the best possible baseline assessment data for comparison to later progress through the study. New analytic tools are being evaluated for consideration of dropouts, missing data, and other hazards of this research. By maintaining records at each stage of the process—from initial screening onward—comparisons are feasible.

Considerable concern has emerged regarding the adequacy of commonly used measures. Psychometrics must be impeccable for obvious reasons but problems do emerge. For example, the authors have found that factor analytic strategies with the POMS may create problems in this field since the factors wash out on careful scrutiny. This may be due to the population on which it was standardized and the comparisons that are being made. In one analysis, using education as a surrogate variable for reading ability, the authors found that the factors can be isolated for those who have a 12th-grade reading level or higher, but not if less education than 12th grade. This suggests that there may be further problems with other measures adapted from other psychiatric populations. Thus, these measures may be inappropriate to detect the changes at a later time.

Beyond this, the utility of using many surrogate measures and attempting to identify predictors must be considered. As previously noted certain key variables such as severity appear to be important while many demographic variables are of limited or no value. At this point, the field would do well to focus on the main task of developing effective treatments for the substance use disorder. While there is rarely such correlation seeking in other areas of medicine, it does emerge in other areas of psychological disorders such as panic and phobias. In these fields there have been calls for a return to the focus on the core disorder, and the advice would seem to apply to substance use disorders as well.

## SUMMARY AND CONCLUSIONS

To summarize, perhaps most important, but most difficult to achieve will be commonalties and standardization across trials so that rigorous comparison is possible. Researchers will do well to examine clinical trials in other areas, mimicking those elements that are compatible, avoiding those that are not, and above all, avoiding costly reinvention.

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# The Addiction Severity Index in Clinical Efficacy Trials of Medications for Cocaine Dependence

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## INTRODUCTION

The Addiction Severity Index (ASI) is a semistructured clinical or research interview (McLellan et al. 1980, 1985, 1992*b*). It was developed more than 15 years ago to fill the need for a standardized, reliable, and valid instrument with which to evaluate substance-abusing patients. More specifically, it was created to enable clinical researchers to evaluate the treatment outcome of drug and alcohol patients. Since that time, it has been widely used and has become a standard. The ASI is used internationally and has been translated into numerous languages. Nationally, a number of States, counties, and cities, in programs that they fund, have mandated the use of the ASI for clinical and program evaluation purposes. Finally, the ASI has become a mainstay in substance abuse research, which is the reason that the role of the ASI in medication trials to treat cocaine dependence is a topic of interest.

Given this kind of popularity, the ASI must have a lot going for it. The ASI is especially valuable as a tool to conduct assessments for clinical purposes and to obtain information to evaluate broad-based rehabilitations. To what extent, however, is the ASI applicable to clinical trials of pharmacotherapy for cocaine dependence? To address this question, first the structure of the ASI will be briefly reviewed. Then the appropriateness and the strengths and weaknesses of the ASI as a baseline assessment instrument and as an outcome measure in clinical efficacy trials of medications for the treatment of cocaine dependence will be addressed.

## OVERVIEW OF THE ADDICTION SEVERITY INDEX

The ASI is a semistructured interview that can be administered by trained interviewers. It assesses patient status in seven areas and obtains demographic information as well. The seven following potential problem areas are evaluated within the ASI: medical, employment, drug use, alcohol use, legal, family/social, and psychological. Questions in each area address lifetime and current functioning (i.e., past 30 days).

Each problem area has several different types of items. The large majority are considered objective items that detail the type, number, and duration of problems and, to a lesser extent, assets. Two more subjective items in each problem area are included: a patient rating of recent problem severity and a patient rating of current need for treatment. The ASI has two summary measures available for each problem area:

1. Interviewer severity ratings are 0- to 9-point estimates of problem severity, defined as the "need for additional treatment." Each severity rating is a subjective synthesis of all the information in a specific problem area.

2. Composite scores (McGahan et al. 1982) are a second type of summary measure and are considered to be more objective indices of problem severity than interviewer severity ratings. Each composite score is developed from a subset of items that reflect current status in a given problem area.

The items are standardized and summed to produce a mathematically derived composite score, which ranges from 0.00 to 1.00 for each ASI problem area. Baseline composite scores and interviewer severity ratings have been found to be highly correlated (Brown et al. 1993; McLellan et al. 1985). The final items in each area are confidence ratings, two items that are interviewer ratings of the veracity of the information elicited from the patient.

The ASI is designed such that it is capable of repeat administration(s), at least 1 month apart, with a followup version that is essentially a subset of items from the full ASI. Composite scores are calculated using the same items in full and followup ASIs. A baseline or admission ASI used in conjunction with a followup ASI(s) can provide a profile of change.

## USE OF THE ADDICTION SEVERITY INDEX TO EVALUATE PSYCHOSOCIAL TREATMENTS

The multidimensionality and breadth of information collected on the ASI are its major strengths as an outcome measure for psychosocial interventions. These strengths are in some ways handicaps when the ASI is used as an outcome measure to evaluate pharmacologic interventions.

Alterman and colleagues (1994) used the ASI as a primary outcome measure to determine the effectiveness of 1 month of inpatient versus day-hospital cocaine rehabilitation. This was a near-perfect fit of the ASI to evaluate a treatment intervention. These two intensive programs, inpatient and day hospital, would be expected to effect change over a number of dimensions (not just cocaine use), and followup evaluations several months following admission would be appropriate (in this case 4 months and 7 months) insofar as treatment effects would be expected to emerge and persist over time. Since these assumptions apply to many psychosocial interventions, it is no surprise that the ASI is a primary assessment instrument in these types of treatment studies for cocaine dependence. Actually, it is a rare study that has evaluated the efficacy of a psychosocial intervention for cocaine dependence that has not used the ASI.

## USE OF THE ADDICTION SEVERITY INDEX TO EVALUATE PHARMACOTHERAPY

### General Considerations

Measures other than or in addition to the ASI may be more appropriate to evaluate the efficacy of pharmacotherapy for cocaine dependence. Medications would very likely be expected to effect change in fewer areas, primarily cocaine use and perhaps psychiatric symptomatology. Change in other areas, for example, criminal behavior, employment status, and interpersonal functioning, would likely be secondary to reduced cocaine use or to any psychosocial treatment coupled with the pharmacotherapy. Furthermore, the timing of pharmacologic and psychosocial treatment effects may be different (Carroll et al. 1994*b*). The medications that have been developed are generally expected to have a rapid onset. Since this is the case, evaluations several months apart or even monthly are not sufficient to capture the course of the treatment effect. At least initially, weekly or more frequent evaluations may be needed to adequately monitor change.

It is important to keep in mind that the ASI was developed as a generic instrument for assessing substance abusers. Therefore, its application to cocaine dependence and more specifically to pharmacotherapy of cocaine dependence will not necessarily address in sufficient detail the nature of the treatment effects. There are actually only three items in the ASI that specifically address cocaine use, i.e., days of cocaine use in the past 30, years of regular cocaine use, and primary route of cocaine administration. One of these items, route of administration, was added in the fifth and most recent edition of the ASI (McLellan et al. 1992*b*), in part because route of administration of cocaine may be an important severity/prognostic variable. A second item, years of regular use, was modified in the fifth edition to include a binge pattern of drug use and not strictly use of three or more times a week. This change was made in part because a typical pattern of cocaine use is bingeing. It is apparent that the ASI does not include important information such as amount of cocaine used and consecutive days of abstinence from cocaine. Furthermore, the interviewer severity rating and composite score for drug use are not cocaine specific. Insofar as these two summary measures of drug use severity are sensitive to and elevated by multiple drug use, they do not necessarily reflect severity of cocaine use.

Weiss and Mirin (1990) have identified four ways in which broad classes of pharmacotherapeutic agents may impact cocaine use. These medications may:

1. Block the effects of cocaine.

2. Treat premorbid, coexisting psychiatric disorders.

3. Treat cocaine withdrawal/craving.

4. Produce aversive reactions following cocaine use.

The ASI does not include items that assess specific variables that may be most relevant to determining whether a medication is producing its anticipated effect. For instance, craving/withdrawal are only addressed on the ASI within the broader item of days of drug problems. Psychiatric symptoms are assessed such that the presence of symptoms such as anxiety and depression are noted, as are the frequency and severity of psychological distress in general. The ASI does not, however, rate the frequency or severity of specific psychiatric symptoms.

This brief review lays the groundwork to outline how the ASI can best be used in clinical efficacy trials of pharmacological treatments for cocaine dependence.

## The Addiction Severity Index as a Baseline Measure

At baseline, the ASI can provide a description of the study sample on a standard set of potentially important background characteristics over and above demographics, such as years of cocaine use, number of previous drug treatments, years of alcohol use, arrest history, and psychiatric symptom and treatment history. Current status in the seven problem areas can also be described with individual items as well as with interviewer severity ratings and composite scores. This information creates a multidimensional profile of the subjects.

The scores on ASI individual items and summary measures can be used to determine whether randomization to treatment conditions has been successful, and in multisite trials to evaluate whether intersite comparability has been achieved. ASI variables can also serve as control variables if important differences do exist. To the extent that the ASI is widely used, it supplies a standard set of variables to compare one investigation with another, and thus provides information that may assist in making sense of conflicting results. The ASI also yields a number of severity variables that can be explored as predictor variables.

As mentioned, the ASI collects valuable background and current status information in seven problem areas, including psychiatric status. It does not, however, elicit the necessary information to determine psychiatric diagnoses. Specifically, although frequency of drug and alcohol use and problems are obtained, the individual diagnostic criteria for substance-related disorders are not assessed. Also, although the ASI has questions about legal history and criminal and violent behavior, it does not supply enough information to make a diagnosis of antisocial personality disorder. Similarly, a positive response to the depression or anxiety items in the ASI psychiatric section does not necessarily indicate a diagnosable mood or anxiety disorder.

It is apparent that there are two general types of information in a baseline assessment that would be a helpful supplement to the ASI. First, psychiatric diagnoses, especially substance-related disorders, are necessary to adequately characterize a study sample. Other Axis I disorders and personality disorders may be important descriptors as well. Second, more detailed information on patients' history and current pattern of cocaine use is recommended.

## The Addiction Severity Index as an Outcome Measure

With regard to the ASI as an outcome measure, the authors have in many ways already alluded to its strengths and weaknesses. The ASI alone does not provide the information to adequately assess outcome in pharmacotherapy studies. The main areas in which more information may be necessary are those concerning cocaine use and problems—amount of use, craving/withdrawal, abstinence, treatment attendance, urinalysis results, etc. Related to this point, Carroll and colleagues (1994*a*) have added a few items to the ASI that, in combination with the standard ASI item "days of cocaine use in past 30 days," can be used to calculate a cocaine composite score. This score is a specific measure of cocaine severity and is unaffected by other drug use (see table 1).

Composite scores and specific items relating to frequency and severity of problems in the seven ASI domains can be compared from admission to varying followup points as measures of change. (Interviewer severity ratings should generally not be used as pre- and postmeasures because they are based on different information at baseline and followup.) For the purposes of pharmacotherapy studies, changes in the ASI problem areas (other than the drug use area), however, are probably best thought of as secondary outcomes. That is, broader changes would most likely be related to a reduction in cocaine use or the psychosocial aspects of the treatment in which the medication is embedded, and not direct results of the medication per se. Insofar as the medications are expected to treat coexisting psychopathology such as depression, the ASI psychiatric scale may be considered a primary outcome measure as well. Nevertheless, in these cases, more syndrome-specific scales may be valuable supplements, e.g., the Hamilton Rating Scale for Depression (Hamilton 1960) or the Beck Depression Inventory (Beck and Beck 1972).

The timeframe reflected in the ASI followup is primarily the past 30 days. If medications are to affect early abstinence, weekly evaluations, at least at first, are probably necessary. The ASI is not designed for such frequent evaluations. There are several other points related to the

**TABLE 1.** *Questions and formula for the cocaine composite score.*

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The cocaine composite score is based on the algorithm for the ASI alcohol composite score.

The cocaine composite includes the first part of question 8 in the ASI Drug and Alcohol Section; i.e., number of days of cocaine use in the past 30. It also requires adding the three following additional cocaine questions to the ASI:

1. How many days in the past 30 have you experienced cocaine problems?

2. How troubled or bothered have you been in the past 30 days by these cocaine problems?__ (Answer = 0-4, not at all - extremely)

3. How important to you now is treatment for these cocaine problems? __ (Answer = 0-4, not at all - extremely)

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The formula to compute the cocaine composite score is as follows:

Cocaine Composite Score = Drug and Alcohol Q8 /120 +
Cocaine Q1 /120 + Cocaine Q2 /16 + Cocaine Q3 /16.

D & A Q8 = number of days used cocaine in the past 30.
C Q1 = number of days problems with cocaine in the past 30.
C Q2 = how bothered by cocaine problems in the past 30 days.
C Q3 = need for treatment for cocaine problems.

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SOURCE: Carroll, personal communication.

timeframe of the evaluation period covered by the ASI. When evaluations are several months apart, the most detailed information collected on the ASI concerns the past 30 days, and that is the information on which the composite scores are based. Regarding the remainder of the followup period, the ASI covers only major events, such as hospitalizations and arrests. Therefore, the course of cocaine use or psychiatric symptoms or alcohol use is not continuously documented unless the ASI is conducted monthly or supplemented by additional timeline followback procedures in the domains of interest. For example, if a baseline ASI and a 3-month ASI followup are conducted, the data available for the comparative analyses are essentially snapshots of the 30 days prior to each evaluation.

In this case, important information such as duration of continuous abstinence and occurrences of relapse episodes is not obtained.

### Measuring the Treatment Context

The ASI does not document the treatment services that patients receive. There are important benefits in evaluating the amount and nature of treatment that patients are receiving during the medication trial. The treatment context within which a medication is delivered may well impact on its effectiveness. The Treatment Services Review (TSR) (Alterman et al. 1993; McLellan et al. 1992*a*) is a structured, technician-administered interview designed to assess the type and amount of treatment that patients receive. In this brief interview, treatment services are categorized along the lines of the seven ASI problem areas. The period addressed with the TSR is 1 week. Repeated TSR interviews can therefore detail the course of a patient's treatment over time. The authors have been focusing on patient variables that can be measured with the ASI. Treatment or program variables, in addition to patient variables and type and dose of medication, may account for individual and site differences in response to medication. The TSR can provide a standard evaluation of treatment services in the same way that the ASI can provide a standard set of patient variables. Therefore the TSR items and summary measures can be used to determine whether patients in different treatment conditions (e.g., active medication versus placebo) are receiving similar levels of ancillary services. In multisite trials, the TSR can be used to determine whether treatment among sites is comparable. The TSR can also supply a standard set of variables to compare one investigation with another. Lastly, the TSR can assist in the effort to determine the overall treatment conditions necessary for a medication to show a therapeutic effect.

## SUMMARY

In sum, the ASI provides a standard and multidimensional initial evaluation of the subject. Furthermore, a profile of subjects is obtained that can be compared at different evaluation points, providing secondary outcomes. However, for the purposes of clinical trials evaluating pharmacotherapy for cocaine abusers, supplemental measures are needed at both baseline and followup to more specifically address cocaine use and problems.

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# Cognitive-Neuromotor Assessment of Substance Abuse: Focus on Issues Related to Cocaine Abuse Treatment

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## INTRODUCTION

Choice of the procedures and types of cognitive-neuromotor testing used in assessment of cocaine abusers and their treatment is dependent on a clear definition of the purposes of testing and the characteristics of the individual tests. This chapter will first discuss published studies of testing in cocaine abusers and pharmacodynamic effects of stimulants and withdrawal. The types of tests available and their characteristics will be discussed in terms of the purpose of testing. The case will be made for the value of computerized cognitive-neuromotor testing when repeated assessment is needed in a busy clinical setting.

Questions to be asked regarding the assessment of cognitive-neuromotor testing in substance abuse are: (1) who is to be tested, (2) at what point in the abuse cycle are the tests to be conducted, (3) what pattern and duration of drug abuse is to be tested, and (4) what is the purpose of testing (e.g., for drug abuser evaluation? for change with therapeutic efforts?). Secondary questions include what is the most appropriate test for assessment and whether there is a means of assessing test sensitivity and stability and establishing external validation. Since this monograph is focused on treatment of cocaine abuse, the authors will primarily explore the effects and questions related to stimulant abuse; examples of the effects other types of drugs of abuse have on testing performance will be presented to highlight differences.

## REPORTED COGNITIVE-NEUROMOTOR CHANGES IN CHRONIC COCAINE ABUSERS

In assessing cognitive-neuromotor testing (CNT) deficits resulting from chronic stimulant abuse, one must differentiate between effects occurring during the initial 1 to 2 weeks of withdrawal and protracted deficits occurring following extended abstinence. Since the turn of the century, clinicians have observed diminished intellectual ability in chronic cocaine abusers. More recently, several groups have assessed chronic cocaine abusers during various times after withdrawal with standardized cognitive-neuromotor testing. O'Malley and Gawin (1990) assessed 25 chronic cocaine abusers who had accrued an average of 135 days of abstinence and whose previous use, over a 4-year period, had been approximately 11 g per month. Compared to matched controls, the cocaine abusers performed worse on cognitive motor skills and simple motor skills, as well as in their composite scores. Deficits were reported in spatial relations, grooved pegboard, grip strength, and retaining nonverbal material. In the same report, a greater impairment was observed during the early abstinence period, suggesting that there was a slight improvement with prolonged abstinence. More recently, Berry and colleagues (1993), assessing over a much briefer abstinence period (i.e., at 72 hours and again at 14 to 18 days) found that, in the first test session, cocaine abusers scored significantly worse than the control group on various measures including visuospatial construction (the Rey-Osterrieth figure), Wechsler Adult Intelligence Scale (WAIS) block design, verbal memory, and concentration. Furthermore, when retested 2 weeks later, the cocaine abusers demonstrated less improvement than controls on measures of psychomotor speed and verbal memory. This finding suggests that selective cognitive deficits are identifiable at least 2 weeks beyond withdrawal. Ardila and colleagues (1991) went further to demonstrate that the duration of previous chronic cocaine abuse was correlated with performance, particularly on the digits subtest of the WAIS, memory quotient, and visual memory of the Rey-Osterrieth figure. In contrast, Manschreck and associates (1990) have reported that, in a group of 33 Bahamian cocaine abusers, most of the mental status features such as intelligence, memory, somatic processing, and motor functions did not differ from controls. The only demonstrable impairment was a decrease in short-term recall of auditory material. In contrast to a number of "paper and pencil" studies cited above, the only computerized neuropsychological testing was reported by Herning and colleagues (1990). They found that both auditory and visual rare event monitoring tasks were not different between patients and control; however, the Sternberg Memory Task appeared to worsen over the course of abstinence. An important caveat to the neuropsychological differences cited above is to what extent there is a corresponding difference in the number of affective disorders and/or attentional deficit disorders; those disorders have been reported, to exceed one-third of the patients who have been receiving treatment for cocaine abuse (see

Rounsaville et al. 1991). Differences in the incidence of affective and/or attentional status certainly could complicate interpretation of cognitive-neuromotor performance results. Moreover, these underlying conditions may require treatment before improvement in CNT performance is observed.

In addition to affective attentional disorders, other medical history of the patient needs to be considered. For example, a history of seizures, strokes, hypertensive crisis, etc., also needs assessment for possible contribution to impairment (Kaye and Fainstat 1987; Levine et al. 1987; Rowbotham 1988; Stein and Ellinwood 1990; Tuchman et al. 1987). Furthermore, the fact that nonspecific cognitive deficits are found in many types of chronic drug abusers, whether due to drug effects, infections, or other medical complications including chronic malnutrition (Bruhn et al. 1981; Carlin 1986; Parsons and Farr 1981), needs consideration. A final caveat is that clinicians report loss of mental energy, incentive, and motivation in the intermediate withdrawal period (see Gawin and Ellinwood 1988 for review), which is difficult to factor out of neuropsychological testing.

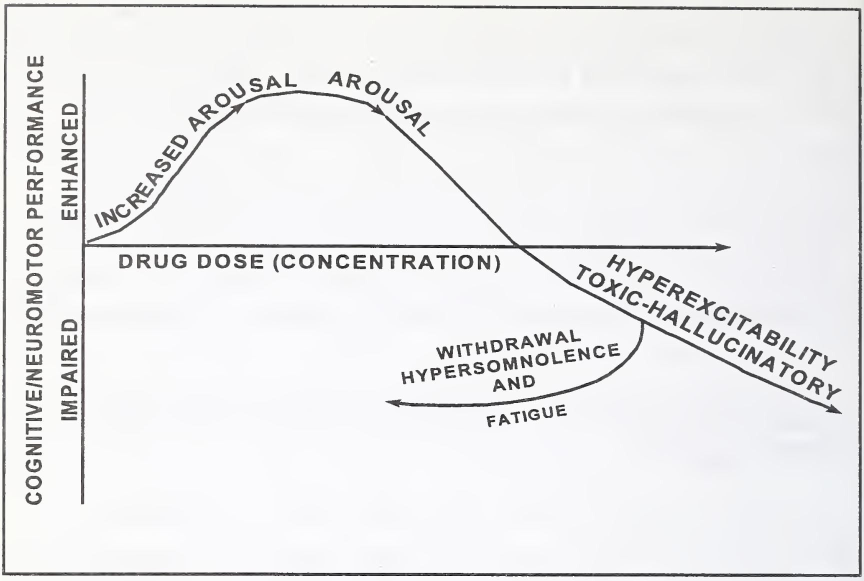
## Acute Pharmacodynamic Effects of Cocaine and Withdrawal

Most assessments of the direct pharmacodynamic effects of stimulants on cognitive-neuromotor skills have been performed with amphetamine or methylphenidate at moderate doses. Stimulants improve WAIS performance including spatial relations, form constancy, visual scanning, visual memory, and short-term recall for learned paired associates (Hurst et al. 1969; Mohs et al. 1978; Rapaport et al. 1978; Weingartner et al. 1980). However, stimulant-induced improvement in performance is specific for moderate doses. Cocaine in moderate doses has also been found to improve vigilance and motor functions in fatigued individuals (Fischman and Schuster 1980). At high doses, stimulants are not effective, especially with complex tasks (MacWorth 1950; Smith and Beecher 1959). High-dose stimulant use can lead to either hyperactive distractibility or highly stereotyped focused attention to details. Although these are opposite effects, both can preclude flexibility in directed attention needed in complex tasks. High-dose use is also associated with more marked withdrawal changes. In addition, because cocaine has a short-effect half-life, an abuser using late into the night or to a point of stimulated exhaustion is also at risk of precipitous withdrawal impairment as the excitatory effects of the cocaine suddenly wear off. Rapid withdrawal may be especially important to vehicle traffic accidents late at night. Prevalence of recent cocaine use in fatal accident drivers (age 16 through 45) was above 15 percent between 1984 and 1987 in New York City (Marzuk et al. 1990). Thirteen percent of drivers stopped for reckless driving in Memphis in 1993 had urines positive for cocaine (Brookoff et al. 1994). A model representation of the relationship of stimulant dosing level as well as withdrawal on performance is shown in figure 1, indicating that both high dosing and withdrawal effects impair performance and judgment. The "crash" withdrawal performance is also further deteriorated by use of alcohol and sedatives to come down from the high (Gawin and Ellinwood 1988).

## COGNITIVE-NEUROMOTOR TESTING FOR THERAPEUTIC DRUG TRIALS

Germane to the theme of this monograph is the consideration that knowledge of stimulant-associated residual impairment is important to the identification and effective treatment in chronic cocaine abusers. In addition, therapeutic drug effects need consideration from two viewpoints: (1) the therapeutic drug may either improve or impair performance, and (2) the interactive effects of the therapeutic drug with subsequent cocaine use may impair performance. Both need consideration for acute and chronic administration of the therapeutic drug.

For Phase I and Phase II studies, initial pharmacological assessment of new central nervous system (CNS) active drugs testing is needed to ensure that it either induces no impairment or that the effect concentration (EC) curve or the 50 percent impairment concentration ($EC_{50}$) is well above the $EC_{50}$ for the therapeutic effect. To accomplish this type of testing the cognitive-neuromotor tests used need to have: (1) a reasonable linear scale of impairment, and (2) the capacity to establish a stable baseline across drug dosing sessions. Tests that assess attentional capacities, psychomotor speed, and coordination most often fit these criteria whereas verbal learning performance does not. The ability to establish a baseline plateau is also important in assessment of actual cocaine abusers undergoing treatment over time, where they can act as their own controls. More difficult to assess is the interactive impairment or even toxic consideration of the treatment drug with subsequent abuse of cocaine. Examples might be catechol-enhancing drugs or drugs with local anesthetic properties (e.g., the tricyclic antidepressants that could potentiate cocaine's potential for toxicity).


COGNITIVE/NEUROMOTOR PERFORMANCE
ENHANCED
IMPAIRED
INCREASED AROUSAL
AROUSAL
DRUG DOSE (CONCENTRATION)
HYPEREXCITABILITY
TOXIC-HALLUCINATORY
WITHDRAWAL
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AND
FATIGUE

**FIGURE 1.** *A descriptive representation of the relationship between the drug concentration and the behavioral effects of stimulants. An initial improvement in performance at lower doses is followed by performance impairment at higher doses and during drug withdrawal.*

SOURCE: Adapted from Ellinwood and Nikaido (1987*b*).

## MERITS OF COMPUTERIZED COGNITIVE-NEUROMOTOR TESTING

In assessment of treatment over time, the neuropharmacologist's task is not unlike that of the industrial environmental toxicologist, i.e., to detect modest changes under conditions where contributions to variance have multiple sources. Thus, using the individual as his or her own control and repeated testing over the period of extended cocaine abstinence (i.e., longitudinal assessment) is important in establishing reliable indices of therapeutic efficacy. A single impaired score flanked by stable baseline scores is likely to indicate a temporary change (e.g., potential recidivism). Usually testing over time involves the use of a battery of tests administered at intervals between testing with one or two reliable performance tasks given more frequently as indicators of changes in the clinical picture (e.g., recidivism). Computer-driven performance batteries, with their capacity to maintain a running profile of the individual's scores over time, certainly facilitate this process and reduce personnel costs dramatically. In addition, computerized batteries of tasks can be presented in a consistent objective manner and can provide ready databases for multisubject and multicenter studies.

Additional merits of computerized batteries need mention. Most paper-and-pencil tests provide summary scores. For example, the powerful component of the WAIS test: digit symbol substitution (DSS), is typically scored as the number of correct answers in a given time period. The version used in the computerized CNT requires the subject to key in the correct number on a telephone keypad as one of the symbols is presented at the bottom of a digital screen; at the screen top the corresponding number-to-symbol code pairs are displayed. Importantly, with computers, the same type of test can provide the reaction time and its profile over the testing period (i.e., learning curve): the number of correct answers, and the composite power score, as well as fluctuations in performance indicating attentional variance. Since DSS is one of the tests with high "G," i.e., tests requiring multiple capacities, these can be fractionated into components. Although DSS provides a powerful screening tool, with additional parallel testing a more definitive breakdown of component capacities is possible. For example, the psychomotor speed component can be obtained by reducing the task to keying in a number that is presented on the screen. When this simple keypad task reaction time is subtracted from the DSS reaction time, an estimate of the central processing speed of the DSS can be obtained. Other versions of the DSS test for posttest memory retrieval of the code by erasing the code from the screen and asking the subject to recall the code pairs from memory.

With appropriate simple transducers and manipulandi, computer testing can assess many neuromotor and sensory components in addition to cognitive function. Extremely sensitive testing of postural stability, eye tracking and saccades, dynamic visual acuity, and hand tremor are some of the tasks available in the task battery in the authors' CNT laboratories. Attentional components are easily tested, including sustained, selective, and divided attention. Other cognitive tasks sensitive to drug effects and easily performed by computers include: Trails A&B various complex or choice reaction time tasks as well as pattern recognition, hidden figure, and memory tests (Ellinwood and Nikaido 1987*a*). Detailed descriptions of many computerized testing systems can be found in the review by Kane and Kay (1992).

In summary, testing with computers is being increasingly used clinically because repeated testing at fairly frequent intervals is a sensitive means of comparing treatment and underlying illness interactions. The specific strengths of computerized procedures include: (1) standardized presentation of stimuli and recording of responses; (2) use of everyday manipulandi (e.g., telephone keypad, car steering wheel), which are familiar to subjects; (3) efficient, accurate, and rapid collection of detailed data components by computer; (4) collection of more precise detailed data or sensory visuomotor and neuromotor function than is usually assessed by qualitative neurological exam; (5) immediate onsite analysis of data and availability to the clinician; and (6) the ease of compiling and analyzing data across subjects and centers.

## EFFORTS TOWARD EXTERNAL VALIDATION OF TESTING

External validation in neuropsychological testing has always presented problems: do tests predict real-world situations (e.g., activities of daily life)? For example, IQ tests in fact have predictiveness for academic performance and job success. Unfortunately, academic and job success data are not readily available from the substance abuser on the "street," whose academic career may have been truncated in early adolescence. In fact, poor school attendance by drug abusers may preclude use of tests such as verbal learning, which are education-level sensitive. Therefore the discussions of the relation of testing to the real world will rely on the driving accident yardstick since even drug abusers are motivated to maintain a driver's license.

Well-documented alcohol studies provide a transitional framework to relate other drugs of abuse induced impairment to: (1) automobile accidents, and indeed (2) the legal limits for blood alcohol concentrations (BACs) while driving are defined. The alcohol accident rate is based on a number of different studies of blood alcohol levels in drivers of both fatal accidents or accidents in general, compared with BACs of drivers in the vicinity who were not involved in the accident (Hurst 1973). By far, the largest study ever accomplished was that of the Grand Rapids, Michigan, analysis where approximately 6,000 blood alcohol determinations from drivers involved in automobile crashes were compared with traffic scene-matched controls. Whereas these data have been analyzed and reanalyzed for potential biases (Hurst 1973), the curves (see figure 2A) indicate that the relative probability of alcohol-related crash is minimal below 0.04 mg/mL BAC, but rapidly increases with higher blood level concentrations. In figure 2B, the laboratory testing with the sensitive digit substitution task shows similar impairment as a function of BAC (i.e., there is a linear relationship between BAC and impairment similar to that of the relative probability of the crash data). Illustrated in figure 2B from a study of eight young, eight middle-aged, and eight elderly subjects (Tupler et al. 1995) are the average change in performance score related to alcohol concentrations. The slope of the curve (figure 2B) is not only very similar to that of figure 2A, but intersects the placebo range at 0.04 BAC, the point in figure 2A in which accident rates begin to rise. At the top of the impairment scale it can be noted that the elderly sample baseline (from which the changed scores are calculated) is very much higher than the alcohol-dosed impairment effects for the young subjects. This indicates the absolute necessity of age-matched controls in any study. Thus, laboratory testing with the "gold standard," alcohol, indicates that the shape of the concentration effect (impairment) curve is similar to what would be predicted from accident rates. Similar results were obtained from several other tasks.

As discussed earlier, the published studies on abused stimulants are sparse. Moderate doses of stimulants actually improve most cognitive-neuromotor performance. Only at the higher stimulant doses or during withdrawal from the higher doses is the marked impairment reported to occur. Obviously, experimental studies with higher doses and chronic stimulant administration present hazards that laboratory researchers cannot risk. Thus, results from safer drugs (e.g., sedative/anxiolytic) studies can serve as examples of potential drugs of abuse to compare with alcohol for relative impairment.

There is extensive experimental literature on benzodiazepine impairment detailing both dose response effects as well as plasma concentration profiles (Gupta and Ellinwood 1995). Figure 3A and 3B compare the effects of the popular benzodiazepines, triazolam and alprazolam, in young and elderly subjects (Nikaido et al. 1990) with alcohol (Tupler et al. 1995). As can be noted, the concentration effect curves for alcohol are marked (see arrow, figure 3) by significant impairment at the legal intoxication concentrations of 0.08 mg/mL and above in both young and elderly subjects. The concentration effect curves for triazolam and alprazolam illustrate that in single doses used clinically (the lower dose for both drugs), there is an impairment equal to or greater than that produced by alcohol at the legal intoxication limit. The other concentration effect curve for alprazolam and triazolam is at twice the highest

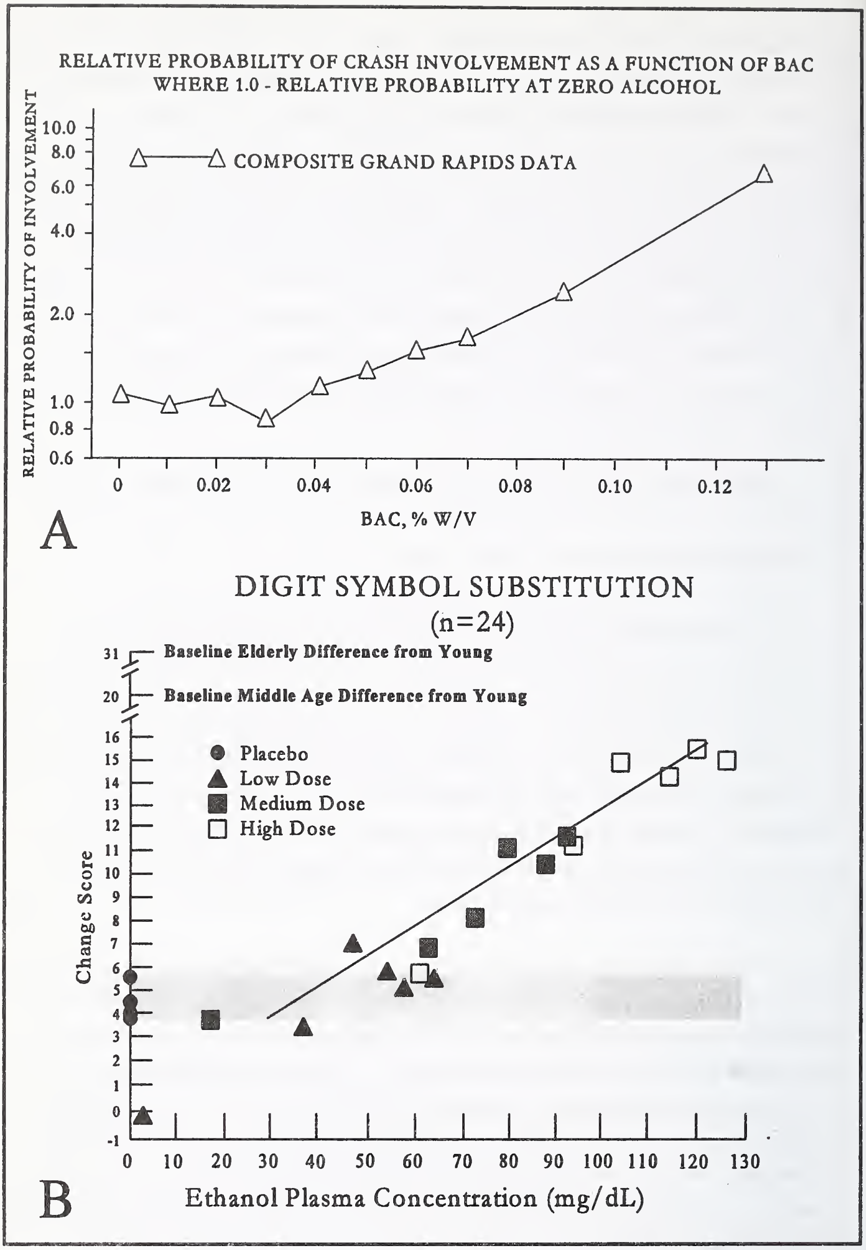

**FIGURE 2.** *Comparison of DSS impairment to accident probability as a function of BAC.*

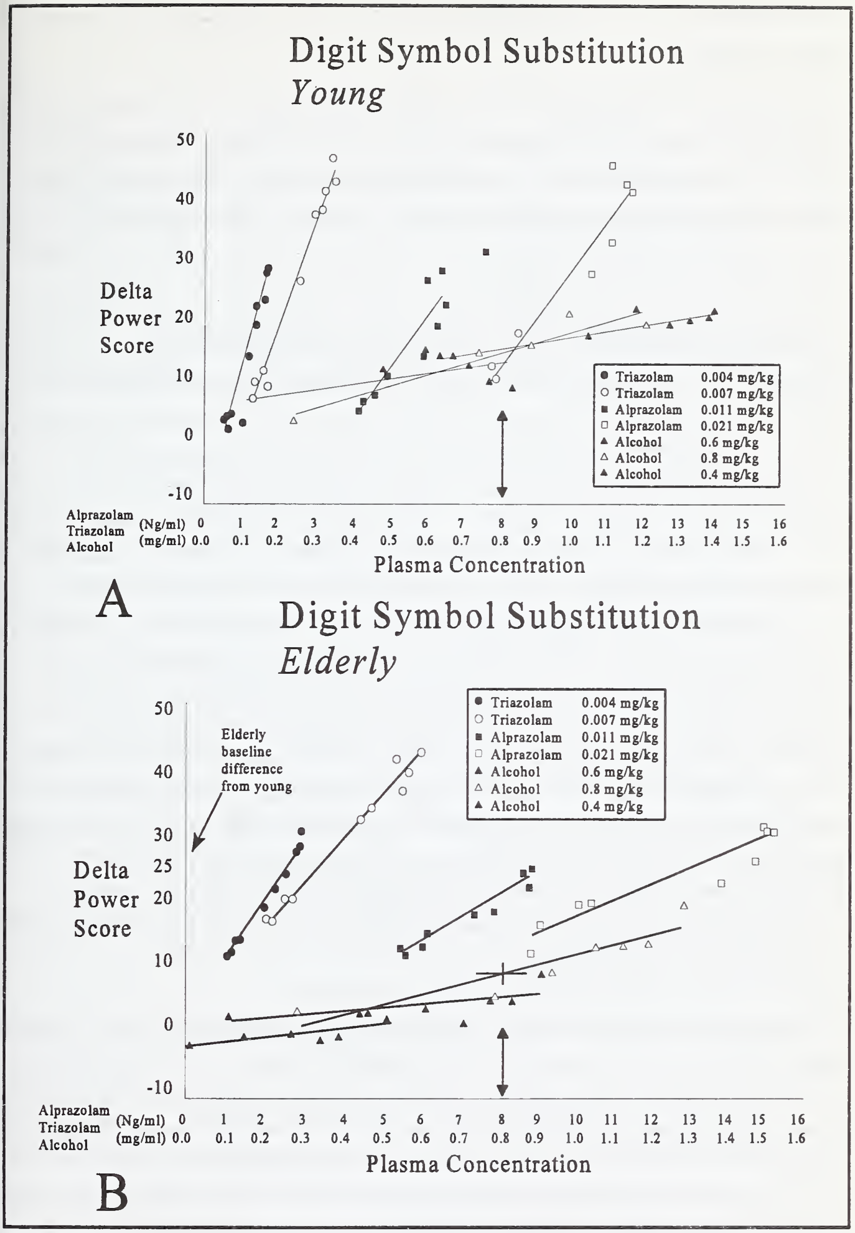

**FIGURE 3.** *Concentration/impairment curves for alcohol, triazolam, and alprazolam in young and elderly.*

recommended dose, comparable to what might be expected with sedative drug abusers.

At the higher dose for these two sedatives, the impairment is well above the impairment found with the legal BAC when driving. The legal alcohol intoxication level was established in the early epidemiological studies demonstrating that 0.10 mg/mL BAC had an accident rate approximately four times that of the control rate (Hurst 1973) and even higher in recent studies (Zador 1991). These impairment studies are similar to impairment findings with on-the-road driving studies (Ray et al. 1993; van Laar et al. 1992; Volkerts and O'Hanlon 1986). Epidemiological studies of driving and benzodiazepine use, although limited, demonstrate an increased risk of crash involvement with the use of benzodiazepines and other anxiolytic and hypnotic drugs. The elevated relative risk of crashes is reported to increase from 1.5 to upward of 4.9 for benzodiazepine and moderate tranquilizer users (Ray et al. 1993). Because it is quite difficult to garner a sample of sedative abusers during the time of their high-dose use, an examination was accomplished with 68 chronic pain patients to compare heavy and light sedative use. Heavy sedative/anxiolytic users were in general more impaired on cognitive-neuromotor tests than light sedative users or no sedative users. Sedative use is defined as muscle relaxants such as baclofen, sedatives, and anxiolytic drugs. In contrast, utilization of the narcotic methadone in chronic pain patients had little relationship to impairment. The authors have also examined driving records of the pain patients involved and found that heavy sedative users have higher incidence of multiple accidents. The heavy sedative abuser sample represented 28 percent of chronic pain patients, yet had 51 percent of all the accidents of pain patients.

With regard to external validation of neuropsychological testing, several indices of cognitive sensory and neuromotor capacity have been related to accident rates. One example is the nondetection of the rapid approach of another vehicle in the peripheral vision (Ball and Owsley 1991). One such selective attention measure known as the useful field of view (UFOV) has been related to accident rates in older drivers. For example, Ball and Owsley (1991) have reported a significant correlation of UFOV impairment with previously reported accidents, especially if the accidents were at an intersection.

Another laboratory measure associated with accidents is selective attention, which requires the ability to both focus as well as shift attention on stimulus locations or salient features. It can be evaluated by such tests as dichotic listening, visual search (e.g., trail-making test), and a cue-directed detection. For example, dichotic listening task errors had a correlation of 0.37 with accident rates over a 1-year period in professional bus drivers (Weiner 1984). A major problem of correlating laboratory tests with accident rates is that accident rates are low-frequency events; thus, the data-relating laboratory tests to driving accident rates remains sparse.

## CHOICE OF TESTS THAT HAVE EXTENSIVE COMPARATIVE DATA LIBRARIES OF NEUROPHARMACOLOGICAL EFFECTS

The types of tasks to be included in a CNT battery obviously are dependent on the particular experimental questions being addressed. The tests included in the CNT battery used at the authors' laboratory were derived from an examination of the literature for tasks most consistently sensitive to drug effects and ones that had the most linear drug concentration effect relationships (see Ellinwood and Nikaido 1987*a*). Actually, the type of test used in the CNT lab and other neuropharmacology labs is very similar to those used by environmental neurotoxicologists. The World Health Organization battery, for example, includes simple reaction time, digit span, digit visual retention, digit symbol, an aiming or coordination task, and a Santa Ana motor coordination task. The reason for using these tests from well-recognized batteries includes the fact that there is a much larger database including normative data with which to relate findings in any given study (Cassitto et al. 1989). In the authors' CNT lab, normative and drug-induced performance data on literally hundreds of subjects have been acquired. Drug classes such as anticholinergic drugs (Nikaido et al. 1990), sedative anxiolytics (Ellinwood et al. 1990; Gupta and Ellinwood 1995; Johnson and Chernik 1982), alcohol (Tupler et al. 1995), etc., have concentration effect curves that can be generated across studies, increasing the size of the background comparison groups. Thus the $EC_{50}$s for new drugs in their early developmental phase can be compared with libraries of other well-documented drugs in young, middle-aged, or elderly men and women for comparison purposes. The use of larger libraries of background data helps considerably when analyzing and interpreting data from a given sample of subjects since age, sex, and genetics all contribute to both the pharmacokinetic and pharmacodynamic variance.

## CONCLUSION

In conclusion, cognitive-neuromotor testing can be utilized in several areas of assessment in cocaine abusers, including: (1) evaluation of residual withdrawal effects of chronic abuse, (2) timecourse of these effects, (3) testing of the acute effects of cocaine and subsequent withdrawal, (4) evaluation of novel early-phase therapeutic drugs for treatment of stimulant abuse, and (5) evaluation of baseline withdrawal impairment profiles of cocaine abusers for the relation to treatment outcome. The choice of the specific cognitive-neuromotor tests to be used in assessments should be made after consideration of pharmacological sensitivity, linearity to dose or plasma concentration, and capacity to establish a stable baseline performance. External validation specific to a drug abuser population will be difficult. In contrast to paper-and-pencil testing, computerized testing allows for the needed reliability and ease of testing in a busy treatment setting as well as facilitating data collection across individuals and treatment sites. Several computerized tasks have current data libraries on drug effects that would provide background information for new studies.

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# Treatment Effectiveness Score as an Outcome Measure in Clinical Trials

*Walter Ling, Steven Shoptaw, Donald Wesson, Richard A. Rawson, Margaret Compton, and C. James Klett*

A variety of measures are used for evaluating patients' responses to substance abuse treatments. These range from physical measures (such as samples of urine, breath, hair, or blood), self-reports of drug use (such as the Addiction Severity Index (ASI) or the Time Line Follow-Back), self-reports of psychological or physiological functioning (such as symptom checklists or craving or mood ratings), and collateral reports. Physical indices of recent drug use, such as urine toxicology screens, are preferable to self-report or collateral reports for evaluating patients' responses to drug abuse treatments because of their objectivity. In order to optimize the likelihood of both detecting individual episodes of problem drug use and correctly inferring drug abstinence based on urine toxicology results, guidelines have been suggested for collection procedures and timing for collection of urine specimens (Blaine et al. 1994; Cone and Dickerson 1992; Jain 1992). However, the difficult task of aggregating urine toxicology results remains, whether when interpreting the response of a single patient to a specific treatment or when evaluating a treatment's effectiveness based on a group of patients' responses in a clinical trial. Difficulties in aggregating urine toxicology results include, but certainly would not be limited to, such problems as the frequency and sensitivity of toxicology screens, early termination of some patients from treatment (or, conversely, the continued participation of some patients who respond poorly to treatment), and problems of analyzing a data matrix that contains a large number of missing datapoints. This chapter reviews the objective indices of treatment response that have traditionally been used and suggests three composite methods for evaluating these data: the Treatment Effectiveness Score (TES), the Joint Probability score (JP), and the Clinical Stabilization Score (CSS).

## TRADITIONAL OBJECTIVE METHODS FOR MEASURING TREATMENT EFFECTIVENESS

Many of the traditional objective measures of treatment effectiveness have been characterized as imperfect indices (Ling et al. 1976) due to their inability to accurately and completely describe the various aspects of treatment response. For example, retention in treatment is one commonly used method for measuring clinical response. However, reliance on retention as a sole indicator of treatment efficacy can be misleading if concomitant use of illicit drugs is not taken into account. A patient who shows little to no alteration in drug use cannot be considered an unqualified therapeutic success regardless of how long he or she remains in treatment.

In addition to retention, clinical reports typically include some type of urine toxicology results to indicate treatment efficacy. Several approaches have been used for interpreting drug use or drug abstinence based on analyzed urine samples. These have included single-point urine test results (such as urine samples collected at posttreatment followup), percent of urine samples during the trial that are negative for drug metabolite, and percent of patients able to achieve a specific criterion (such as a varying number of consecutive weeks of samples negative for drug metabolite).

Most commonly used to document long-term followup status, single-point urine samples can detect recent drug use, but cannot indicate patterns of drug use throughout the followup interval. Further, patients who provide urine samples at followup are usually those who can be located, which further increases the threat to the internal validity of this treatment response indicator. Still, many trials of substance abuse treatments will include long-term followup urine results as a primary indicator of treatment efficacy.

Clinical trials of substance abuse treatments depend on urine toxicology results gathered during treatment to evaluate efficacy. Researchers have debated the merits of using qualitative versus quantitative values for interpreting urine toxicology results (Cone and Dickerson 1992). However, these data are most commonly reported as percent of samples negative for the metabolite of the problem drug. Simple percent-negative indices can provide some indication of patients' overall response, but do not characterize accurately those patients who terminate early despite all samples being negative for metabolite or those who remain in the trial, yet continue to use the problem drug. One alternative to a simple percent-negative index is the achievement of a specific criterion based on achieving some number of consecutive weeks of negative urinalysis (Carroll et al. 1991; Higgins et al. 1991) or percent of patients with continued abstinence. Criterion-linked indices can suffer from the problem of setting cutoff levels. That is, liberal cutoff levels can inflate the actual clinical utility of a specific treatment, while conservative cutoffs can underrepresent treatment efficacy. There are at least two other problems associated with this approach. One is the loss of ability to discriminate among patients with various drug use patterns, e.g., using an 8-week criterion in a 16-week trial would count each of the following patients as a success: (1) a patient who consistently gives drug-free urines for 16 weeks; (2) a patient who uses drugs at the beginning of the trial but then "cleans up" and gives drug-free urines for the last 8 weeks; and (3) a patient who initially is fully compliant, gives consistently drug-free urines for 8 weeks, and then relapses to drug use or drops out of the program altogether. A second problem is that the use of such a criterion yields a noncontinuous (i.e., categorical) dependent variable that is not optimal from a statistical point of view.

All traditional approaches to interpreting urine toxicology results are vulnerable to the effects of missing data. At a minimum, missing datapoints are a nonrandom influence on the data matrix. Further, missing data likely indicate treatment inadequacy—patients typically do not attend a clinic regularly when treatment is ineffective. Missing data heavily influence single-point urine results since the reason for the missing data cannot be accurately represented in subsequent analyses. It is often unknown whether missing data are due to patients' resolution of their drug problem, to patients' continuing drug use, or to patients' refusal to participate. By contrast, percent-negative urinalysis methods can overrepresent patients' responses when patients discontinue treatment early but provide all samples negative for drug during the trial. Least affected by missing data are estimates of achievement of specific criteria, since patients with missing data usually fail to meet the specific criteria.

Traditional methods for interpreting objective clinical indices also commonly focus on one indicator to the exclusion of others. Synthesis of information that describes patients' treatment response (as measured by urine toxicology), treatment compliance (as measured by retention), and treatment toleration (as measured by lack of severe side effects/toxicity) allows for a more complete evaluation of various aspects of the efficacy of a given treatment. Dissatisfaction with the limitations of traditional methods for interpreting objective measures led the authors to experiment with new ways to compile and interpret these data to address specific concerns that have been encountered while conducting clinical trials.

## NEW METHODS OF INTERPRETING OBJECTIVE MEASURES OF CLINICAL RESPONSE

### The Treatment Effectiveness Score

One important concern for any trial is objective evidence of treatment efficacy. As an alternative to the methods reviewed earlier for interpreting retention and urine data, the authors developed the TES, which is a different approach to interpreting retention and urine toxicology results with conceptual advantages. Using the TES, “clean” urines rather than “dirty” urines can be counted. This simple shift emphasizes patient success rather than failure, but avoids the explicit imputation of a missing specimen as “dirty.” That is, a patient either provides a “clean” urine as scheduled, or does not. “Clean” urines are counted for the full scheduled tenure of each patient in the trial.

For example, in a study of 17 weeks’ duration requiring three urine samples each week, there would be 51 scheduled urine specimens. If each “clean” urine earns a point, a metric is established with a range of 0 to 51. The most successful therapeutic outcome is represented by a patient who attends the clinic reliably, completes the full duration of the trial, gives urine specimens as requested, and whose urine samples are consistently clean. Such a patient would obtain a score of 51. Patients may achieve scores of less than 51 in two ways: either by providing one or more urines positive for the drug of abuse being tested or by providing fewer than 51 specimens due to missed clinic visits or leaving the trial early. The TES provides a measure of relative standing in comparison to other patients in the trial. In the above example, each patient has the opportunity to earn 51 points by complying with the therapeutic expectations.

Conceived in this way, sample attrition is not a concern. Every patient who is randomized has a score and is included in the analysis. There are no dropouts in the usual sense and there is no assumption of whether or not patients who are no longer actively participating have returned to illicit drug use. Within a single clinical trial, there is no need to convert the score to a percentage because all patients have the same denominator, although doing so facilitates comparison across studies of different duration or different scheduling of urine collection. It is important to understand that the TES is not a pure measure of illicit drug use, nor is it a measure of retention, although it is heavily influenced by both. It is also influenced by other clinically important parameters such as adherence to clinic policy, drug craving, and withdrawal symptoms, to the extent that these affect retention and drug use. Thus, the TES is intended as a composite score that reflects multiple aspects of therapeutic success.

The authors have applied the TES to data gathered as part of two large pharmacotherapy trials. In an opiate pharmacotherapy trial, the TES was compared with the more commonly used percent of urine samples negative for opiate metabolite (Ling et al., in press). Results of comparisons of patients' responses to different opiate medication treatment conditions using the two indices showed similar patterns when using the two measures. This similarity of results indicates that the TES can provide a valid alternative to percent-negative urine samples yet also captures retention. The advantage of the TES over the percent-negative urine samples is that this measure provides a clear indication of treatment response: averaged TES scores represent the expected value of negative urine samples for similar patients who receive an identical treatment.

The TES has also been applied to urine toxicology data generated from a cocaine pharmacotherapy trial and has been found to correlate significantly with traditional objective and subjective measures of treatment outcome (Ling et al. 1995). Specifically, the data showed the TES to exhibit significant positive associations with the percent of patients who achieved criteria of 3 and 8 consecutive weeks of urine samples negative for cocaine metabolite, with the average number of weeks of retention, and with the average number of counseling sessions attended by patients. Significant negative associations were found between the TES and the ASI drug scale and the Profile of Mood States (POMS) depression score (McNair et al. 1992).

These findings provide strong evidence for the validity of using the TES as an outcome indicator of clinical response. Application of the TES to data from these two large pharmacotherapy trials has indicated that the TES is a conceptually encompassing and succinct indicator of outcome. Implicit in its measurement, the TES provides an indication of another important factor: patients' acceptance of the treatment. Patients can reject treatment for a variety of reasons that range from resumption of drug use, to being incarcerated, to resolution of the drug problem. Assumptions of "automatic positive" for missing data when using traditional methods for interpreting urine toxicology results are avoided with the TES. By not imputing the cause of missing data, the TES simply interprets missing data as an indirect measure of patients' acceptance of the treatment.

While the TES is an improvement over unidimensional scores, it is not perfect. There will always be a few patients who are unable to complete the trial for reasons beyond their control and for reasons that have nothing to do with the treatment. However, the authors' current position is that early termination is either drug related or it is random. A relatively few random events could distort trial results, but this risk seems preferable to layers of assumptions that might have the same effect. It is obvious that information about drug use during the trial is lost whenever the vector of test results is collapsed into a single score. Patients with the same score can have different drug use profiles with quite different therapeutic or prognostic implications. The authors are interested in this and intend to explore other approaches.

## The Joint Probability Score

Another limitation of traditional outcome measures involves the lack of a conceptually linked method for understanding the clinical relevance of the trial. A method for estimating a given patient's probability of successful outcome at a specific point in time would be useful to both clinicians and researchers. Most reports of clinical trials customarily present a retention curve and an illicit drug use curve as a means for summarizing objective treatment response data. Using these to estimate patients' responses can result in biased appraisals, since both of these indicators are vulnerable to nonrandom influences. Although broad statements about the value of a particular treatment can be inferred for a group of patients, such retention and drug use aggregate estimates cannot provide accurate information about the probability of treatment success over time.

One method for compiling retention and illicit drug use data that approaches the purpose of estimating patients' response is to plot the number of samples negative for illicit drugs during a given week divided by the number of scheduled urine tests for that week times the number of patients still active in the trial (Ling et al., in press). This technique intends to correct for patients who terminate participation early, though plots of such data are likely to demonstrate a gradual upward trend, which a casual reader might interpret as clinical improvement in patients. Such an association is likely to be spurious, since in most clinical trials the number of patients who terminate early increases over time, and attrition in this group is likely not due to a random process. Rather, dropouts are more likely to be those patients who have more severe levels of drug dependence and/or who show poor response to the treatment than those who resolve their dependency or who have external forces that preclude continued participation. Thus, plots that illustrate the performance of the residual sample will likely show an upward trend since those remaining in the trial are those who tolerate the treatment and who may show positive treatment responses.

A correction to this problem is to multiply each point of the plot described above by the probability of retention to that point. In essence, the plot is converted to a JP curve. For example, in a trial requiring one sample per week, the point at week X would be $p_1$ (i.e., the number of patients still in the study at week X divided by number of patients who started treatment) times $p_2$ (i.e., the number of urines negative for illicit drugs at week X divided by the number of patients still in the study at week X). Since the numerator of $p_1$ and the denominator of $p_2$ cancel out, the curve can be constructed simply by dividing the number of negative urines obtained each week by the number of patients who started the study. This curve will tend to take a downward path unless the loss of patients over time is fully compensated for by better performance of the residual sample. As presented, the JP is a conservative measure of treatment efficacy in a clinical trial. Upward drift over time can be attributed to the effectiveness of the treatment program rather than to influences on the data of differential dropout of treatment nonresponders.

Validated using data in a large opiate pharmacotherapy trial (Ling et al., in press), the JP has yet to be applied to data from clinical trials of cocaine or other drug abusers. However, the logic underlying the JP index argues for its use in trials using these other drug-dependent patients. Knowing the retention rates, the number of samples negative for illicit drugs over the weeks of a trial, and the original number of patients, researchers and clinicians can easily calculate accurate probabilities that their patients will produce a negative urine sample at a given point when using a specific type of treatment. Plotting the JP index produces a curve that can also be useful in comparing outcomes from different studies of the same medication.

## The Clinical Stabilization Score

The need for a composite index of treatment response, retention, and acceptance has been identified by the authors when conducting dose-ranging studies of new medications for substance abusers. In such trials, information that describes the safety and efficacy of a particular medication at a particular dose level is crucial, yet often incomplete. Measurements of good therapeutic response to a medication should a priori indicate the elements that demonstrate that response. The CSS is an index developed by the authors to address this point.

The CSS is based on a set of criteria devised to study therapeutic responses to variable doses of medications in the treatment of drug dependency. As the name implies, the CSS is used to indicate that a specific dose of a specific medication has stabilized the patient's drug dependence problem. The criteria that comprise the CSS are based on a logic that incorporates clinically important elements of the patient's response to medication: reduction of illicit drug use, continued treatment compliance, lack of adverse symptoms, and absence of drug toxicity. CSS criteria are framed in a 2-week time period. The window of observation moves forward in real time as the patient remains in the trial. The clinical assessment consists of three elements:

1. *Urine toxicology.* Monitored urine samples are collected at a set rate over the course of the clinical trial. Samples are collected on Mondays, Wednesdays, and Fridays, with no substitutions allowed. Urine samples are immediately analyzed (within 24 hours) for the presence of metabolite of the problem drug. The sample must be free of this drug for the patient to earn a CSS point.

2. *Clinic attendance.* To earn a CSS point, patients must attend the clinic as scheduled on a Monday, Wednesday, or Friday. Patients who receive a CSS point comply with treatment. Conversely, patients unable to comply with treatment likely will not attend clinic and, hence, cannot earn a CSS point.

3. *Adverse signs and symptoms.* At each occasion for submitting urine samples, the patient must report that he or she is free of moderate to severe medication-related or withdrawal-related symptoms and

adverse medical events to earn a CSS point. For a drug abuse medication to be clinically useful, it cannot induce symptoms or effects that produce moderate to high levels of discomfort in patients. Patients who report moderate to high levels of adverse signs and symptoms cannot earn a CSS point.

Using these criteria, the authors provided the opportunity for patients to earn CSS points three times per week, which corresponds with each occasion for providing a monitored urine specimen. Patients must achieve all three CSS criteria (come to the clinic, provide a drug-free urine specimen, and be free of moderate to severe symptoms) to achieve one CSS point. Using the scheduled visits in the authors' research, patients can earn a possible six points over any 2-week period. Patients who earn five or six out of the six possible CSS points in a 2-week period, and who earn one of those points on the most recent assessment occasion, are considered to have stabilized on a therapeutic dose of medication. Study designs that use different numbers of assessment points per week will have correspondingly different ranges of possible CSS points. However, the rolling 2-week period for evaluating CSS scores should be retained.

The CSS is not conceptualized as an outcome evaluation tool for comparison among patients. Rather, it is a measure of how well a given dose of study medication is helping a particular patient reduce his or her problem drug use, without causing untoward symptoms and adverse effects. In a clinical pharmacotherapy trial, the CSS can be used in dose runup phases of studies or in studies that have variable medication levels to monitor patient safety and to trigger study medication dose changes. Unless a satisfactory CSS is achieved (e.g., a CSS of five or six out of the six possible points), the dose of study medication is increased by one increment at each weekly review. If the occurrence of adverse symptoms reduces the CSS, the medication is not increased or may be decreased by one increment. If a satisfactory CSS is achieved, the dose remains unchanged.

It is conceivable that some patients could show positive response to a study medication such that good therapeutic response can be maintained with less frequent clinic attendance than the three times per week required by the authors' studies. Further, good therapeutic response may be affected by a medication, though some patients may find it inconvenient to attend the clinic on scheduled days. The CSS would be unable to discriminate between such instances and poor response to medication.

Another problem is that the CSS suffers from all indices that use a cutoff for classifying response outcomes. For some patients, four of six scheduled urine samples being negative for illicit drugs over a 2-week period could be classified as a treatment "success." At this point, the authors are planning to evaluate the sensitivity and specificity of various cutoff levels using the above criteria for the CSS. Finally, the CSS was conceived as an index to address needs specific for a certain type of pharmacotherapy trial and has been used by the authors for this purpose.

## CONCLUSIONS

It is agreed that objective methods for assessing patients' responses to clinical trials offer the best indication of treatment efficacy. However, the authors maintain that traditional methods of interpreting such data are imperfect. Development of alternative methods for interpreting objective data should be driven by researchers' needs to understand various aspects of treatment response during the trial. The three indices suggested in this chapter are intended to provide empirically derived integration of retention and urine toxicology measures to indicate treatment outcome (TES), probable treatment response (JP), and good therapeutic response (CSS). Although these indices are still in the development and evaluation phase, they offer clear advantages to traditional methods for assessing patients' responses in clinical trials.

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# Pharmacokinetics of Cocaine: Considerations When Assessing Cocaine Use by Urinalysis

*Reese T. Jones*

## INTRODUCTION

Changes in a patient's patterns of cocaine use are generally considered an important outcome measure of treatment efficacy. Other treatment outcome measures are important as well, but if a treatment does not stop or significantly decrease the intensity of a cocaine addict's cocaine use, many would question the treatment's efficacy. Examination of a patient's urine for evidence of cocaine or cocaine metabolites is an objective index of cocaine use. Like many biochemical measures useful in medical practice, urinalysis to measure cocaine or its metabolites, although relatively simple and straightforward from an analytic standpoint, is subject to misinterpretation and erroneous conclusions if the underlying biological principles are not properly considered.

This chapter considers selected aspects of cocaine clinical pharmacology, particularly cocaine pharmacokinetics as it applies to the use of urinalysis to measure treatment outcome in cocaine addiction treatment trials. The focus will be on examination and assessment of urine, though cocaine and its metabolites are also measurable in other biological media—hair, sweat, saliva and, of course, blood. Saliva, hair, and sweat offer advantages in terms of accessibility but have not been sufficiently studied to fully understand the biodisposition and kinetics of cocaine. At this time, there are insufficient data to make proper quantitative interpretations. Consideration of future use of hair and saliva assays to measure cocaine use and discussion of assay procedures in general are included elsewhere in this volume.

The pharmacokinetics and metabolism of cocaine make for easy monitoring of illicit cocaine use in most clinical situations. Typical patterns of use result in substantial levels of cocaine and metabolites in urine. A variety of immuno- and chromatographic assays make quantitative urine measures relatively easy compared to other drugs of abuse. Cocaine is taken by a variety of routes. In the United States, cocaine is most commonly smoked or snuffed, but it is also used intravenously, particularly by individuals likely to enter treatment research programs. Some kinetic considerations are route dependent. Smoking in particular has special attributes (Jones 1990).

## PHARMACOKINETICS AND METABOLISM

Cocaine hydrochloride, a crystalline salt, is commonly snuffed or injected. Cocaine base (crack) is the form usually smoked because the base is more volatile, vaporizing at a lower temperature, in contrast to cocaine hydrochloride, which decomposes before it volatizes when heated. Cocaine is a weak base with a pKa of 8.6. In its basic form in blood and smoke, cocaine crosses cell membranes quickly and efficiently. Like nicotine in tobacco smoke, cocaine, when it reaches the small airways and alveoli of the lung, is rapidly absorbed into the blood. Although cocaine's pulmonary kinetics are not as well studied as nicotine, rapid absorption of cocaine through the lungs, presumably because of the large surface area of the alveoli and small airways, probably accounts for the appeal of that route of administration.

The rate and the relative amount of cocaine entering systemic circulation depend greatly on the route of administration. Figure 1 illustrates differences in time of peak plasma levels of cocaine when approximately equipotent doses were administered to the same 10 volunteer subjects by different routes. Absorption from nasal mucosa when snuffed and absorption from mouth and the gastrointestinal tract when taken orally are similar and much slower than after smoking or after intravenous (IV) administration (Jeffcoat et al. 1989; Jones 1990). Peak plasma levels occur on average about 60 minutes after nasal or oral intake; though, like many attributes of cocaine kinetics, individual variability is great, ranging from 30 to 120 minutes in different individuals. An individual's kinetics vary between laboratory sessions as well. Oral and nasal bioavailability are both about 30 to 40 percent, though variability is greater by the oral route.

Like nicotine in cigarette tobacco, cocaine has smoked bioavailability of between 10 and 20 percent, more commonly the lower amount with typical smoking devices. When cocaine is smoked, the relatively low and variable bioavailability is a consideration if attempts are made to infer cocaine dose consumed by examination of only urine concentrations.

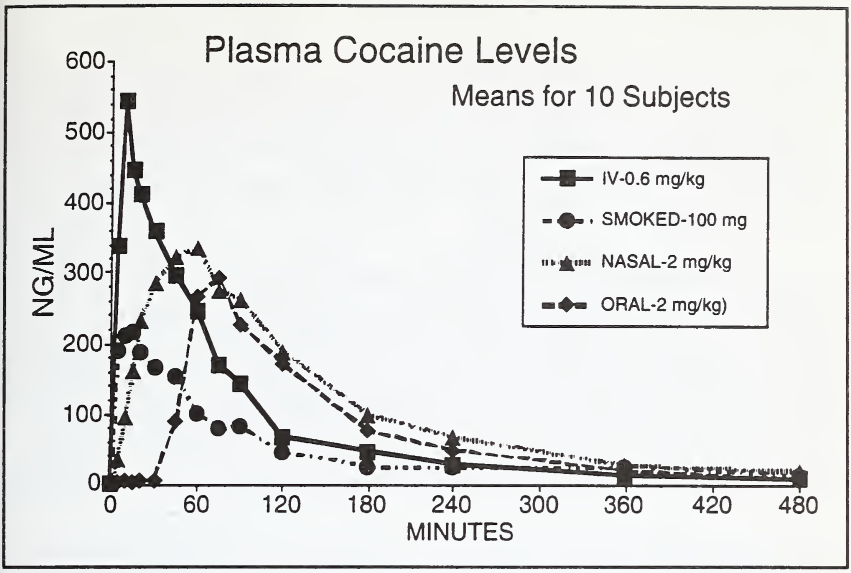

**FIGURE 1.** *Plasma levels of cocaine after dosing by different routes.*

A patient may report buying and putting considerable cocaine in a pipe and smoking it, report experiencing intense effects, and yet show less benzoylecgonine (BE) in urine assays than an IV or nasal user (Jones 1990).

Peak venous blood concentrations and, by inference, peak arterial blood levels after self-administered doses of cocaine vary enormously. Not only do cocaine doses vary but, with IV administration, rate of injection is as important a determinant of peak cocaine levels in blood as is total dose. Cocaine doses commonly range from 0.2 to 3 or 4 mg/kg, depending on route. Peak plasma levels can range from 50 to 2,000 ng/mL or greater, depending on route and rate of injection. Peak arterial blood levels of cocaine should be several times higher than venous levels when cocaine is smoked or taken intravenously (Chiou 1989).

Cocaine, after intake, is widely distributed through body tissues. Volume of distribution usually ranges between 1.5 to 2 L/kg (Ambre et al. 1988; Jeffcoat et al. 1989). Cocaine is rapidly metabolized. Major metabolic pathways are by enzymatic hydrolysis to BE or ecgonine methyl ester, then to ecgonine (Ambre et al. 1988). About 1 to 5 percent of a cocaine dose is excreted unchanged in urine. Cocaine is rapidly cleared from plasma, but variably, at 20 to 30 mL/min/kg. Elimination half-life of cocaine is similarly variable, averaging 1 to 1.5 hours. BE elimination half-life is 6 to 8 hours. Ecgonine methyl ester half-life is 3 to 8 hours.

Metabolic pathways are illustrated in figure 2. Hydrolysis to BE accounts for about 45 percent of a dose (Ambre 1985). Enzymatic hydrolysis to ecgonine methyl ester accounts for approximately the same or slightly less. Neither BE nor ecgonine methyl ester has significant biological activity in humans. Norcocaine is a potentially active metabolite but occurs in only small and probably pharmacologically insignificant amounts in humans.

Cocaine and ethanol are commonly consumed at the same time by the majority of people who use cocaine regularly. In the presence of ethanol, cocaine is transesterified by liver esterases to ethyl cocaine, also called cocaethylene (Dean et al. 1991). Cocaethylene has cocaine-like pharmacologic properties. Cocaethylene is measurable by the same techniques used for assaying cocaine in urine, saliva, hair, or sweat, as are the ethyl homologs of BE and ecgonine ethyl ester.

When smoked, the cocaine pyrolyzes to a number of chemicals depending on temperature (Martin et al. 1989). Anhydroecgonine methyl ester (AEME), also known as methyl ecgonidine, can be measured in the urine of people who have smoked relatively small amounts of cocaine (Jacob et al. 1990). AEME does not appear in the urine after injection or snuffing. Thus, if treatment-related changes in typical route of use are of interest as a treatment outcome measure, it might be possible to objectively measure by urinalysis a patient's shifts from or to cocaine smoking. Thus, in principle, even typical routes of use and concurrent use of alcohol can be measured. The human pharmacology of AEME has not been studied, but in animals it is pharmacologically active.

BE is the commonly assayed metabolite for monitoring treatment outcome. With most commercially available assays, BE can be detected in urine for 3 to 4 days after last cocaine use. The detection duration obviously depends on the amount of cocaine used in the recent past, on the definition of the cutoff value required before reporting the presence of BE, and on assay sensitivity.

## ROUTE OF ADMINISTRATION

Route of administration can also determine amount of cocaine entering the body and thus the amount of BE in urine. Figure 3 shows mean plasma

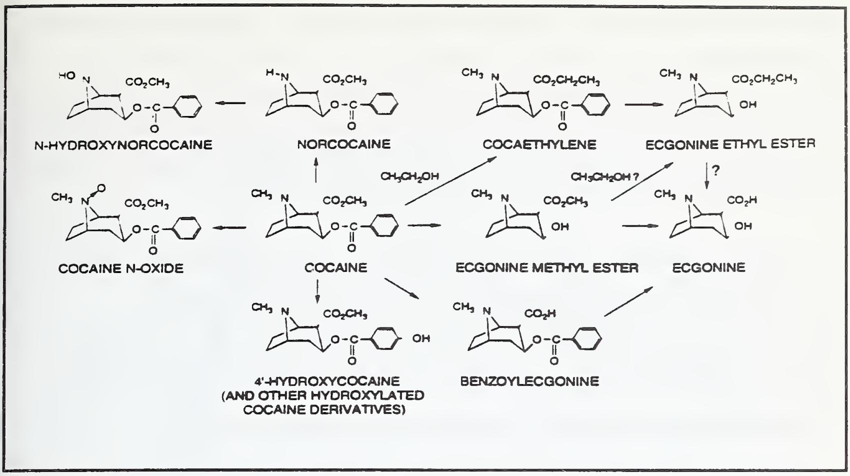
N-HYDROXYNORCOCAINE
NORCOCAINE
COCAETHYLENE
ECGONINE ETHYL ESTER
$CH_3CH_2OH$
$CH_3CH_2OH$ ?
?
COCAINE N-OXIDE
COCAINE
ECGONINE METHYL ESTER
ECGONINE
4'-HYDROXYCOCAINE (AND OTHER HYDROXYLATED COCAINE DERIVATIVES)
BENZOYLECGONINE

**FIGURE 2.** *Metabolism of cocaine, including pathways when ethanol is present.*

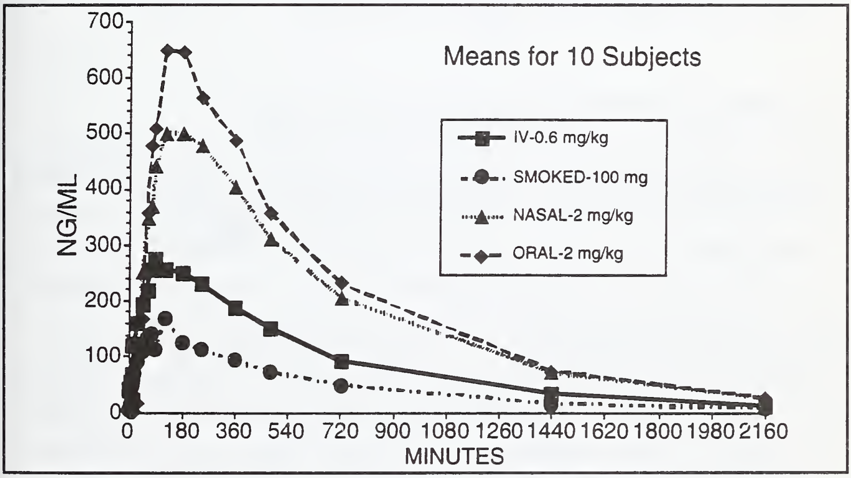

**FIGURE 3.** *Plasma levels of benzoylecgonine after dosing by different routes.*

BE levels from the same 10 subjects as in figure 1. The higher maximum concentrations and greater area under the time concentration curve (AUC) after the nasal and oral doses of cocaine are typical. Smoked doses of cocaine, though producing more intense transient effects, result in relatively smaller amounts of cocaine actually absorbed into the body; hence, smaller peak levels and AUC for BE.

Although the plots in figure 3 represent BE levels after only a single dose, and are from plasma rather than urine, they illustrate the importance of considering route of administration when inferring patterns of cocaine use from urine (or plasma) concentrations alone. Smoking, because of the relatively low bioavailability, often results in smaller absorbed amounts of cocaine after each smoked dose and results in relatively lower levels of BE when compared to fewer but larger doses of nasal cocaine or IV doses of cocaine. Of course, increased numbers of smoked doses over whatever time is being considered could change this pattern, but the principle holds; other things being equal, a cocaine smoker may have relatively lower levels of BE in urine than someone snuffing cocaine or using cocaine intravenously.

## PHARMACOKINETICS AND COCAINE DOSE

Taking only a single dose of cocaine is not a characteristic pattern of use in the real world. A session of illicit cocaine use often involves taking multiple doses over many hours. One approach for administering doses of cocaine closer to real-world conditions is by use of sustained infusions. Figure 4 illustrates mean BE levels in urine during and 48 hours after a 4-hour continuous infusion of IV cocaine hydrochloride given to a group of 10 nondependent volunteers hospitalized on a hospital research unit. All had extensive experience with IV use. The plotted values are midpoints of 12-hour collections of total urine output. In test sessions spaced 2 days apart, subjects received over the 4-hour infusion total cocaine doses of 105 mg, 210 mg, 420 mg, and a placebo infusion. The cocaine doses were administered as 0.3, 0.6, and 1.2 mg/kg loading doses followed by constant rate infusions at a rate calculated to equal previously determined clearance.

The 420 mg dose was judged by all 10 subjects as very high and close to exceeding what they could comfortably tolerate during a typical session

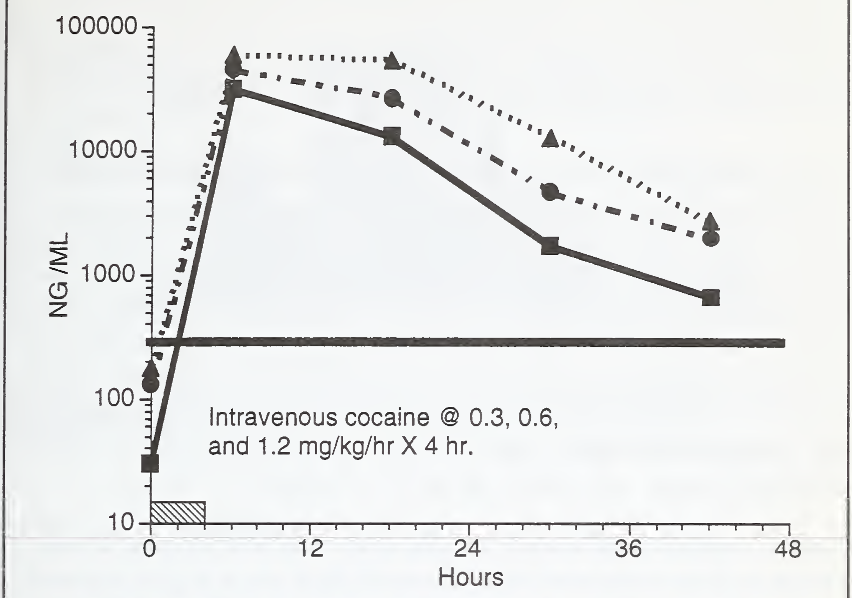

**FIGURE 4.** *Urine levels of benzoylecgonine during and after a 4-hour infusion. Plotted values are midpoints of 12-hour urine collections.*

of self-administered cocaine. During the 420 mg dose, toward the end of the infusion, three subjects became very restless and showed hints of beginning delusional thinking. None of the subjects described the effects of that dose as a pleasant experience. In contrast, the lowest dose (105 mg) was judged by most subjects as less than they would have liked. The effects were described as less than typically experienced during a session of self-administered use.

Each of the doses was significantly different in effects and in BE AUCs and plasma concentrations during the log linear phase of clearance. However, if a 300 ng/mL cutoff criteria was used for determining positive or negative urines, the three very different doses would appear equal at 48 hours, i.e., all urines were still positive. By a least square fit for the log linear phase, the lowest dose would have become negative at about 49 hours, the medium (210 mg) dose at about 60 hours, and the highest (420 mg) dose at about 65 hours. If an investigator's goal was, by some treatment or other, to decrease total amount of cocaine use during a user's typical session of cocaine use, then quantitative urinalysis would distinguish the three different dose exposures at almost any point after cessation of cocaine use. A qualitative (positive or negative) urine test would not distinguish unless daily tests were performed.

In this study, there was no evidence of dose-dependent differences in clearance. The maximum levels of BE in urine were in the range of levels commonly encountered in cocaine addicts participating in treatment trials. The data indicate that, with a 300 ng/mL cutoff criteria, patients who have used cocaine for 4 hours or so during a single evening can test positive 60 hours later. Although the plot in figure 4 does not show individual variability, in fact there was little variability between subjects. Cocaine levels in urine showed more between-subject variability, as might be expected with a drug where urine pH might have greater effect on clearance.

Another method to administer cocaine doses that result in urine levels similar to those associated with real-world illicit use is to give repeated doses under controlled and close medical supervision. Figure 5 illustrates urine cocaine and BE levels from one of nine volunteers given repeated 140 mg oral doses of cocaine hydrochloride every 4 hours during the period beginning on day 7 and ending on day 11. Twenty-four hour urine collections began on the first day of admission to the University of California General Clinical Research Center and continued each day, 0800 to 0800, until discharge on day 21. The kinetics of the oral cocaine doses approximated nasal doses. While on this 840 mg/day dose schedule, urine levels of BE were approximately 100,000 ng/mL; levels not unlike the BE concentrations measured in the urine of some cocaine addicts in treatment trials. Cocaine levels in urine during the period of repeated oral doses were about 3,000 ng/mL and also in the range observed in cocaine addicts in treatment.

When the oral doses of cocaine were replaced by placebo capsules late in the afternoon of day 11, the 24-hour urine BE concentrations decreased over the next 3 days. Noteworthy in this typical patient was that by the third day after cocaine administration stopped, by criteria commonly used in treatment trials (a 300 ng/mL cutoff), the patient would probably have tested negative for BE with a urine sample containing 180 ng/mL.

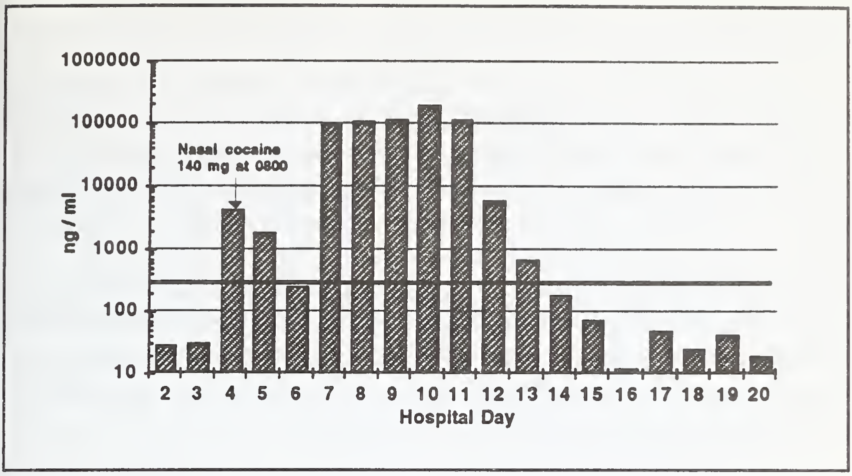

**FIGURE 5.** *Benzoylecgonine levels in 24-hour urine collections. The hospitalized subject received oral cocaine, 840 mg daily, on days 7 through 11, and single nasal doses of cocaine, 140 mg, on day 4.*

Only 3 days before, this individual was markedly intoxicated by cocaine while receiving doses of cocaine similar to daily doses associated with binge-type use behaviors. If a quantitative assay was used, in this instance gas chromatography with mass spectrography with cutoff of 10 ng/mL, the patient had measurable BE 9 days after the last dose of cocaine. The increase in BE levels on day 4 resulted from a single 140 mg nasal dose of cocaine. That single dose produced very modest effects and also was followed by a negative urine 2 days later, if a 300 ng/mL cutoff criteria was applied. The point is, using nonquantitative urine criteria there was only 1-day difference in changing from positive to negative after a single, pharmacologically trivial dose of nasal cocaine as compared to the urine change after cocaine doses that produced a period of sustained and pharmacologically intense effects.

## HOW MUCH BENZOYLECGONINE IS IN AN ADDICT'S URINE?

After becoming aware of typical urine levels of BE after cocaine administration in conditions that partially mimic the real world of cocaine use, as illustrated in figure 4 or figure 5, it seemed important to determine what urine concentrations might be in typical cocaine addicts participating in treatment trials. Curiously, no one had bothered to measure actual concentrations of BE in urine despite the enormous amount of money and time spent on nonquantitative urine assays in treatment trials. It was well known that patients arriving in emergency rooms with cocaine-related medical complications not uncommonly had urine BE levels over 100,000 ng/mL, but nothing was known about actual levels in typical cocaine addicts in treatment programs (Batki et al. 1993). Gas chromatographic quantitative assays of urines from cocaine addicts in treatment trials showed that urine BE levels above 10,000 ng/mL were common and 22,562 ng/mL was the median value for a group of 16 patients just entering treatment. Patients with urine levels of 100,000 ng/mL or more were not unusual. Occasional patients with urine BE levels as high as 300,000 ng/mL did not report any noteworthy acute toxicity or unusual cocaine-related events.

The pharmacokinetic data on cocaine and BE levels in urine collected in the author's research laboratory experiments with nonaddict, cocaine-using volunteers are remarkably congruent with the real-world urine levels in a cocaine treatment clinic. In light of typical urine BE levels of 10,000 to 100,000 ng/mL, routine application of a 300 ng cutoff to define positive or negative (or clean or dirty) urines may be a little shortsighted and holds cocaine treatment trials to a higher standard for determining a clinically significant change than is commonly applied in other medical treatments. For example, consider a patient who had been using cocaine almost every day and enters a treatment trial with urine levels of about 100,000 ng/mL of BE. The patient would test positive for urine BE. After 8 weeks' treatment if the patient was still using some cocaine almost every day but taking much smaller doses, and if the patient had levels of 310 ng/mL at the time of testing, the urine still would be reported as positive if judged by binary criteria and the patient might be termed a treatment failure despite a 99.7 percent decrease in the amount of cocaine used. Most treatments in medicine that change maladaptive behavior or symptoms by 99.7 percent would be considered successful.

## SPECULATIONS ABOUT HISTORY AND RATIONALES

One argument for the binary urine assessment strategy is that quantitative urinalysis is more time-consuming and more costly. However, considering the total cost of a typical, well-designed Phase II clinical treatment trial and the hidden costs of falsely accepting a treatment that later turns out to be less useful, the true cost differences may not be as great as assumed. Worse yet, consider missing significant decreases in amount of cocaine use in a treatment trials and thus falsely and prematurely rejecting a promising treatment. In medical practice, it is rare for a quantitative biochemical test, particularly one that may be important in clinical decisionmaking, to be judged on a simplistic binary positive or negative report. Drug abuse research almost stands alone in using such data as an outcome measure.

Perhaps the original justification for the use of binary assessments was a common treatment goal in addiction treatment research: achieving total abstinence. However, if an acceptable treatment goal is fewer occasions of cocaine use or use of a lower dose or a more acceptable route on each occasion of use, then consideration of the pharmacokinetics of cocaine becomes important when using urinalysis to measure treatment outcome.

Until recently, most cocaine addiction treatment trials used the same urinalysis methods and the same rationale when interpreting urinalysis results as were developed for detecting or following illicit cocaine use in the workplace or for clinical monitoring, mainly to make therapeutic decisions regarding illicit drug use in opiate addiction treatment programs. The assays generally were immunoassays for BE. Because of concerns about cross-reactivity and resulting false-positive reports, a common practice was to specify a 300 ng concentration cutoff for BE. Any sample with a BE concentration below 300 ng/mL was reported negative or a clean urine. A sample with BE concentration above 300 ng/mL was reported a positive sample (or a dirty urine).

Selection of the 300 ng/mL cutoff did not involve any formal consideration of cocaine's pharmacokinetics. In fact, when currently popular cutoffs were established, there were no data on typical BE levels in the urine of cocaine users entering treatment trials. The 300 ng/mL cutoff was largely determined by committee, with considerable input from marketing and legal advisers, as a compromise to minimize false-positives and limit, to an acceptable number, false-negatives in workplace testing programs. Given the goals of typical workplace testing programs (zero tolerance for any cocaine use), absolute or upper levels of BE in a urine sample were irrelevant. Whatever workplace sanctions imposed as a consequence of urine test results were the same at 325 ng/mL as at 100,000 ng/mL levels. To apply the same logic when establishing an appropriate cutoff in a clinical trial may be inappropriate.

## CONCLUSIONS

Of what practical value is information on cocaine kinetics for someone designing or evaluating a treatment trial outcome and considering urinalysis data? Patients participating in treatment trials might typically enter with concentrations of 100,000 or 200,000 ng/mL of BE in their urine. How long BE would be measurable after complete abstinence, of course, depends on assay sensitivity or the selection of cutoff criteria. With commonly available gas-chromatographic assays, sensitivities of 10 to 100 ng/mL are not unreasonable. A patient might have measurable BE in urine 5 days after last use if an assay sensitive to 10 ng/mL is used. If the clinician chooses to or has to discard some of the potentially available quantitative data and instead applies some higher cutoff (200, 300, 400 ng/mL), then obviously the window of urine positivity following complete abstinence narrows considerably.

BE concentration in urine is a dose-dependent quantitative measure of systemic cocaine dose actually delivered. In contrast, addict self-reports of money spent on cocaine or reports of days cocaine was used are subject to greater error due to bioavailability considerations, memory impairment related to cocaine-induced delirium, unreliable underestimation or overestimation, or deliberate lying. Cocaine dose differences as small as 100 mg are distinguishable (see figure 4). With daily urine measures, even the taking of a single 140 mg nasal dose is detectable for 1 or 2 days after use. With frequent enough urine sampling, changes in urine BE levels accurately reflect very small changes in dose patterns, assuming some measure of the usual pattern of dosing. Since frequency and amount of cocaine use per time unit are interrelated, BE assays will never completely distinguish dose frequency from dose amount. However, for estimates of the amounts of cocaine used over a 24-hour period, the pharmacokinetic data indicate that reliable estimates of dose are possible.

How the pharmacokinetic information might best be applied depends greatly on treatment goals. If total abstinence is the treatment goal, then whatever the assay, whether semiquantitative or quantitative, a very low cutoff used to define the urine as negative is most desirable. A 300 ng/mL cutoff may be too high if abstinence is the treatment goal. If urine samples are obtained only two or three times a week, and the patients are other than regular daily users, episodes of cocaine use will be missed if a 300 ng/mL cutoff criteria is applied. If a treatment goal is to significantly decrease cocaine use in terms of typical dose used or frequency of dosing, then quantitative urine BE assays obtained as frequently as possible would be the ideal continuous variable to measure that aspect of outcome. How frequently urines can be obtained depends on the clinical setting and research budget. The best advice would be to obtain urine samples as frequently as possible—daily if possible. Any frequency of urine sampling less than daily will tend to underestimate the frequency of use and typical dose used over days or weeks.

An individual addict's cocaine taking is a behavior as complicated as any other behavior. A single snapshot or sample of a behavior at any point in time cannot give an accurate representation of complicated behavioral patterns over the previous few days or week. A urine sample every day is probably more than is necessary to track small changes in cocaine-using behavior. However, even a cursory consideration of cocaine pharmacokinetics suggests a single weekly urine sample is not enough and even every-other-day sampling will miss small fluctuations. Measurement of BE levels in urine offers an objective, quantitative, biological measure of treatment outcome; to some extent clinical researchers can get from it what they are able to afford.

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# Quantitative Urine Levels of Cocaine and Other Substances of Abuse

*Jeffery N. Wilkins*

## INTRODUCTION

Quantitative urine levels of cocaine and other substances of abuse hold the promise of providing new and important information that goes beyond the scope of qualitative results. This chapter describes clinical and treatment research applications of quantitative urine levels of substance abuse analytes. A historical review is presented, caveats are discussed, and a single-step dilution Abbott ADX/TDX method is provided. Examples are presented that support the utility of quantitative urines in pharmacotherapy trials of cocaine and other substances of abuse, in health services research, in studies of polysubstance abuse, and in studies associating biological markers with phases of physiological dependence and risk to relapse.

By tradition, substance abuse urine results are expressed in qualitative terms of positive or negative. However, urine levels of substance of abuse may also be expressed with quantitative/scalar values. For example, a patient's urine level of the cocaine metabolite benzoylecgonine (BE) can range from 0 to 300,000 ng/mL or higher. The numerator of a quantitative urine analyte level contains either a measure of weight of the respective analyte (e.g., ng) or its molarity (e.g., µmol). The denominator contains either a measure of urine volume (e.g., mL) or the amount of excreted creatinine (Cn). Cn is employed as an indicator of renal clearance since it is a byproduct of cellular metabolism excreted steadily by the kidney and not reabsorbed through the renal tubule. Analyte adjustment with Cn compensates for dilute or concentrated urine resulting from the patient's fluid intake. Cn adjustment is helpful in a number of circumstances, including when a patient has ingested large volumes of liquid, perhaps in order to defeat the urine test. A Cn-adjusted level is produced by dividing the concentration (mg/mL) of excreted Cn into the analyte concentration. As an example, Cn values of 0.5 and 2.0 mg/mL would adjust a BE level of 100,000 ng/mL to 200,000 ng/mg and 50,000 ng/mg, respectively.

## BACKGROUND

Quantitative urine levels of lead and other toxins, adjusted for urine dilution, have been employed in the fields of environmental and industrial medicine for 50 years (Levine and Fahy 1945, reviewed by Elkins and Pagnotto 1974). In the early 1970s, smoking cessation investigators embraced the quantitative method and Cn adjustment for expressing urine levels of the nicotine metabolite cotinine (reviewed by Sepkovic and Haley 1985). Yet, despite the long-standing recognition of urinalysis as a critical tool in the treatment of substance abuse (Harford and Kleber 1978), only a limited number of substance abuse investigators have employed quantitative urines.

Manno (1986) described how replacing qualitative results with Cn adjusted quantitative urine levels of the carboxy metabolite of delta-9-tetrahydrocannabinol prevented both false-positive and false-negative interpretations of cannabinoid use (see figure 1). Additional publications have supported this position for cannabinoids (Bell et al. 1989; Lafolie et al. 1991), as well as cocaine (Weiss and Gawin 1988, Wilkins et al. 1994*a*), opioids and benzodiazepines (Lafolie et al. 1991), and buprenorphine, a mixed agonist/antagonist opioid (Watson 1992). Weiss and Gawin (1988) noted that quantitative urine BE levels allowed for differentiation of positive BE levels arising from washout, from positive BE levels resulting from new cocaine use. The demonstration of protracted BE washout in cocaine-using patients (Burke et al. 1990; Cone and Weddington 1989) amplifies the need to distinguish washout from new cocaine use in clinical practice and research.

## SINGLE-STEP DILUTION PROTOCOL

Table 1 outlines a single step dilution protocol for the determination of quantitative urine BE levels, based on the Abbott ADX/TDX Net P value (Wilkins et al. 1994*b*). The Net P value is inversely proportional to the analyte concentration (see figure 2), representing the intensity of polarization/fluorescence produced by the sample. Since the Abbott ADX/TDX printout provides the Net P value in all of its assays, the dilution protocol can be applied to a number of substance abuse analytes (see table 2). For example, the initial Abbott ADX/TDX run of a sample presumably containing BE will produce a numeric value from 0 to 5,000, or the printout will state “greater than 5,000”; i.e., out of the Abbott

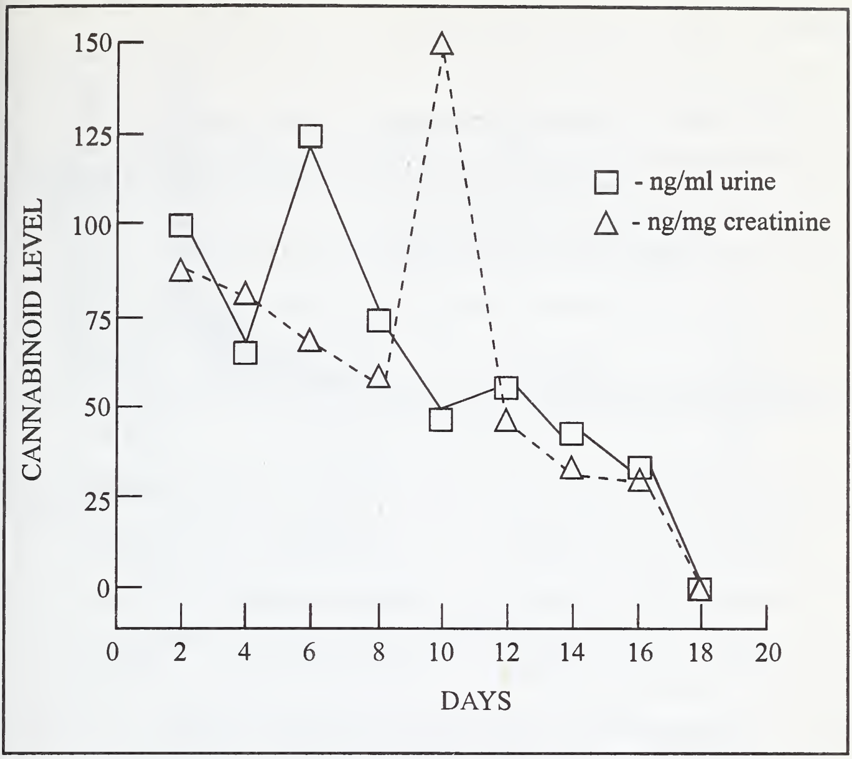

**FIGURE 1.** *Urine levels of the carboxylic acid cannabinoid metabolite in one patient. When the cannabinoid metabolite is expressed as ng/mg of excreted creatinine, a false-positive interpretation is avoided on day 7 and a false-negative interpretation is avoided on day 11.*

SOURCE: Manno (1986).

assay range. In this latter case, a dilution step and subsequent rerun of the assay is required. The single-step dilution protocol provides BE values to 150,000 ng/mL (a maximum dilution of thirtyfold times 5,000), a range that includes most sample values and identifies new cocaine use in most circumstances. If following the dilution step the Abbott printout again reads "greater than 5,000," this indicates that the BE value is > 150,000. The author's laboratory generally employs 150,000 as its maximal reporting value since a second dilution step significantly increases the range of dilution-based error and routine clinical needs do not require values beyond 150,000 ng/mL. When it is desirable to

**TABLE 1.** *One-step dilution protocol.*

1. First, analyze undiluted sample.
2. Do not dilute if within assay range (i.e., < 5,000 ng/mL for BE).
3. If exceeds assay range, dilute as follows using Abbott buffer.
4. Mix sample before taking aliquot and mix diluted sample well before assay.
5. Can adjust final result by dividing by excreted creatinine.

| 1st run Net P | Dilution* | Sample Volume | Diluent Volume |
|---|---|---|---|
| 75-80 | 1:3 | 100 μL | 200 μL |
| 70-75 | 1:5 | 100 μL | 400 μL |
| 60-70 | 1:10 | 100 μL | 900 μL |
| 50-60 | 1:20 | 100 μL of 1:10 | 100 μL |
| 40-50 | 1:30 | 100 μL of 1:10 | 200 μL |

KEY: * = Repeat sequence if postdilution result is > 5,000.

NOTE: The one-step process dilutes samples up to a maximum of 150,000 ng/mL (generally over 90% of samples encountered in a pharmacotherapy trial).

produce values over 150,000, a second dilution step is performed according to the same steps employed for the first dilution. Once a diluted value is produced, adjustment with Cn can be performed.

Using samples obtained from a pharmacotherapy trial of cocaine abuse/dependence (Margolin et al. 1995), the reliability of the single-step dilution protocol was evaluated by comparing final BE concentrations with the levels predicted by the Abbott ADX/TDX Net P values. Almost all of the 1,619 samples (97.5 percent) were diluted correctly by the procedure. The validity of the single-step dilution protocol was evaluated by split-sample comparisons of Abbott's fluorescence polarization immunoassay (FPI) method with high-pressure liquid chromatography (HPLC) and diode array detection according to a modification of Svenson (1986). Across 26 random samples, a Pearson

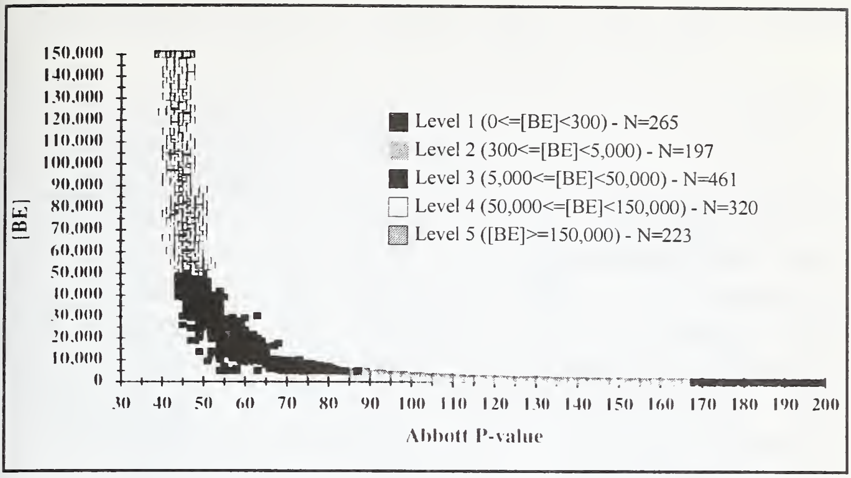

**FIGURE 2.** *Relationship between initial Abbott net P values and diluted semiquantitative urine BE levels in 1,466 samples from 48 patients. 93% of levels were > 100,000 when Net P was <42; 96% of levels were > 40,000 when Net P was < 46; 96% of levels were > 20,000 when Net P was < 55.*

correlation of 0.992 was demonstrated between the FPI and HPLC methods. Once urine BE levels exceeded 150,000 ng/mL, the FPI values were consistently higher than the HPLC values, producing an across-sample variance of 11.79 percent.

## HEALTH SERVICES RESEARCH

Quantitative urine levels for substance of abuse have been used to define the prevalence of substance use in the week prior to admission in patients admitted to psychiatric inpatient programs at the Veterans Administration Medical Center (VAMC) West Los Angeles (Shaner et al. 1993; Wilkins et al. 1991). Quantitative urine levels have also been used to define the cascade process that begins with a mentally ill patient's use of a substance of abuse and ends with hospitalization (Shaner et al. 1995). In this latter study, serial quantitative urine BE levels from 155 schizophrenic patients were analyzed to track new cocaine use. New use was defined within 3-day intervals. The results demonstrated a clear relationship between receipt of disability pension money, subsequent cocaine use, the development of cocaine-associated psychiatric symptomatology, and subsequent admission to the hospital.

**TABLE 2.** *Application of single step dilution protocol to Abbott Assays of abusable substances other than cocaine.*

| | Predilution upper limit of assay | New upper assay limit following thirtyfold dilution |
|---|---|---|
| Amphetamine class[1] | 8,000 | 240,000 |
| Amph./methamphetamine II[2] | 8,000 | 240,000 |
| Barbiturates II U | 2,000 | 60,000 |
| Benzodiazepines | 2,400 | 72,000 |
| Benzodiazepines serum | 2,400 | 72,000 |
| Cannabinoid | 135 | 4,050 |
| Cocaine metabolite | 5,000 | 150,000 |
| Ethanol (urine) | 300 | 9,000 |
| Methadone | 4,000 | 120,000 |
| Opiates | 1,000 | 30,000 |
| Phencyclidine II | 500 | 15,000 |
| Propoxyphene | 1,500 | 45,000 |

KEY: [1] = Includes both dextro and levo isomers of amphetamines.
[2] = Assays only dextro isomer of amphetamine and methamphetamine.

The investigators are continuing to use quantitative levels to evaluate the impact on cocaine use from treatment interventions based on contingency management.

## POLYSUBSTANCE ABUSE

Serial collection of quantitative urine levels can be used to track sequences of polysubstance abuse. As an example, opioid and cotinine levels have been compared across time using Box-Jenkins Time Series analysis (Wilkins et al., in review, see figure 3). These results suggest that cigarette smoking and opioid use are behaviorally linked.

## QUANTITATIVE URINE LEVELS AND BIOLOGICAL MARKERS OF SUBSTANCE ABUSE

Biological markers may prove clinically useful in characterizing a patient's level of physiological dependence as well as risk to relapse

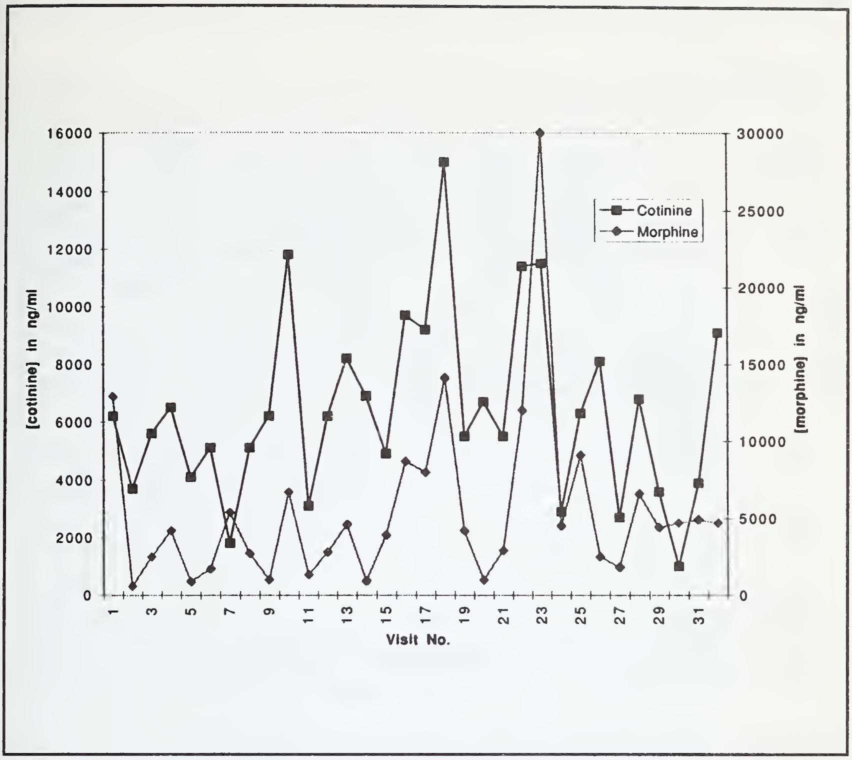

**FIGURE 3.** *Parallel patterns of semiquantitative urine levels of cotinine and morphine for one buprenorphine-maintained patient across 11 weeks (i.e., 32, three per week visits). Across all visits, the Box-Jenkins autocorrelation value was 0.57.*

once abstinent. Preliminary data suggest that quantitative urine levels may be useful as covariates in identifying endogenous substance abuse-associated biological markers. At a 1-year followup of patients treated for cocaine abuse, circulating levels of cortisol and prolactin (HPrl) were found to vary according to the range of the quantitative urine BE level (Wilkins et al. 1992; figure 4). Cortisol levels reached their highest elevations when urine BE reflected a later stage of abstinence (i.e., < 200 ng/mL > 0) and returned to baseline when BE was no longer present in the urine. Circulating HPrl levels were at their lowest when BE levels reflected recent cocaine use (i.e., > 50,000 ng/mL), increased when BE levels reflected early abstinence (i.e., > 10,000 ng/mL), and, unlike cortisol, remained elevated above baseline even when BE levels were no longer present. The cortisol results suggest that patients

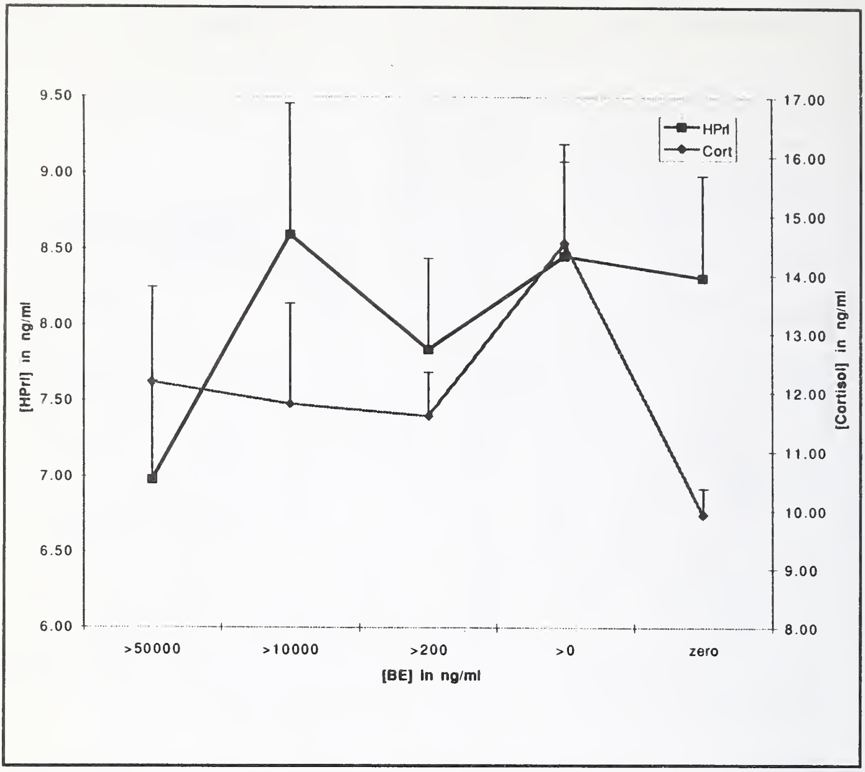

**FIGURE 4.** *Circulating cortisol and prolactin in 191 patients categorized according to semiquantitative urine levels of BE. Blood and urine were collected between 9-10:30 a.m. as part of a 1-year followup for patients previously treated for cocaine abuse/dependence. The number of samples for each BE category is as follows: >50,000 (14), >10,000 (24), >200 (35), >0 (19), and zero (99).*

experience a significant stress response approximately 3 to 4 days after initiating abstinence from cocaine. Relatively lower HPrl levels at the earliest stages of abstinence are consistent with inhibition of HPrl release secondary to cocaine-induced increases in hypothalamic dopamine. Subsequent elevations of HPrl, as abstinence from cocaine progresses, are consistent with previous studies demonstrating elevated HPrl during most phases of cocaine abstinence (Dackis and Gold 1985; Mendelson et al. 1988). In sum, these preliminary results suggest that HPrl and cortisol may serve as biological markers of the varying stages of abstinence from cocaine.

## PHARMACOTHERAPY TRIALS OF COCAINE ABUSE

Quantitative urine levels of abused substance may become an important adjunctive measure in pharmacotherapy trials for cocaine and other substances of abuse. Based on their ability to detect changes in amount and frequency of cocaine use (Li et al. 1995), quantitative urine levels may be used to screen potential subjects, assist in determinations of sample size power analysis, and provide pre- and postmedication outcome comparisons.

Inclusion criteria in substance abuse pharmacotherapy studies are employed, in part, to assure that study patients are selected from the same population. Quantitative urine levels may distinguish a study population based on baseline substance use. For example, although the two patients represented in figure 5 would meet conventional study inclusion criteria for cocaine use based on qualitative urines positive for BE (i.e., > 300 ng/mL), quantitative urine levels reveal a fiftyfold variance between the patients in baseline BE levels. According to their baseline cocaine use, these potential subjects may not represent the same population. Thus, inclusion of both patients into a pharmacotherapy trial as equals may introduce confounds contributing to a Type II error.

Premedication quantitative baseline levels may also be helpful in power analysis determinations. For example, quantitative urine BE values are substantially different for the two populations demonstrated in figure 6. Although both groups are made up of cocaine-using, methadone-maintained patients, significantly different research designs may be required to test for medication effect in each population. Total abstinence might be the goal for the population with 56.7 percent positive urines, whereas a consistent diminution in urine BE levels might be the endpoint for the population with 90.8 percent urines positive for BE.

In addition, quantitative urine levels have been proposed to serve as a primary outcome variable in pharmacotherapy trials for cocaine abuse (Batki et al. 1993). The author notes that qualitative urine measures would have failed to recognize a potential therapeutic effect of fluoxetine for the treatment of cocaine abuse. The study results, confounded by elevated premedication BE levels in the placebo group, raises a number of timely questions including whether it is useful to identify medications that do not necessarily produce complete abstinence but reliably reduce cocaine use and frequency.

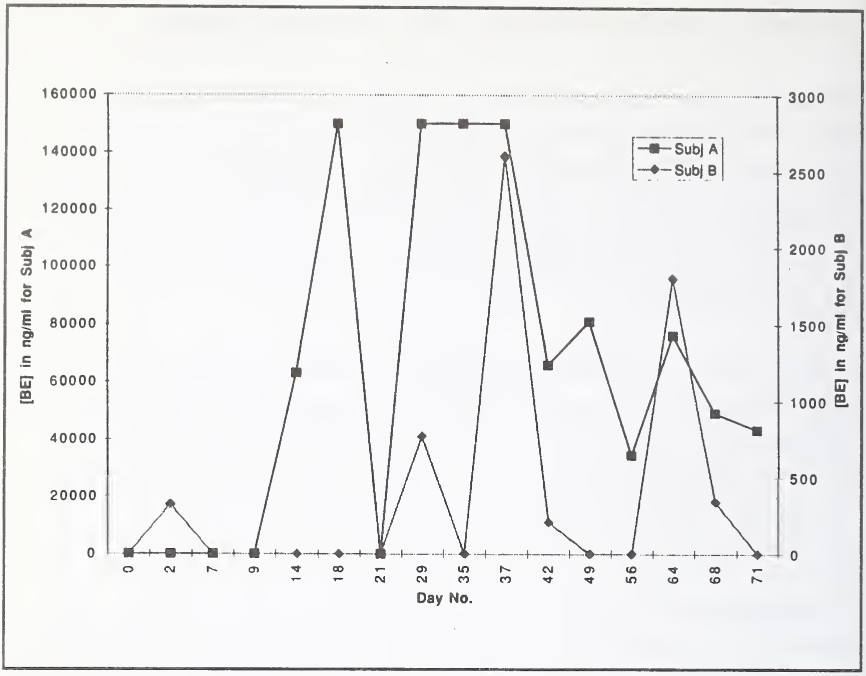

**FIGURE 5.** *Semiquantitative urine BE levels in two cocaine-abusing subjects. Urine levels from subject A are approximately fiftyfold higher than those in subject B.*

## CAVEATS

Despite the strengths offered by quantitative urine levels, research investigators and clinicians need to proceed with caution when interpreting the clinical significance of the levels. Tracking of quantitative urine levels does not definitively demonstrate the dose, time of drug usage, clinical condition and/or behavioral impairment at the time of sample collection (Jatlow 1992), despite careful and thorough evaluation by Ambre and colleagues (1991). Quantitative and qualitative urine results are influenced by variance in the appearance of substance abuse analytes in urine (see reviews by Catlin et al. 1992, Chiang and Hawks 1986, and Osterloh 1993) resulting from interindividual differences in frequency and amount of substance used, the presence of contaminants in the substance, route of administration, sex, race, age, weight, diet, metabolic enzyme activity (e.g., cholinesterase activity for cocaine), rate of excretion, formation of condensation products (e.g., cocaethylene in users of cocaine and alcohol), drug interactions, and

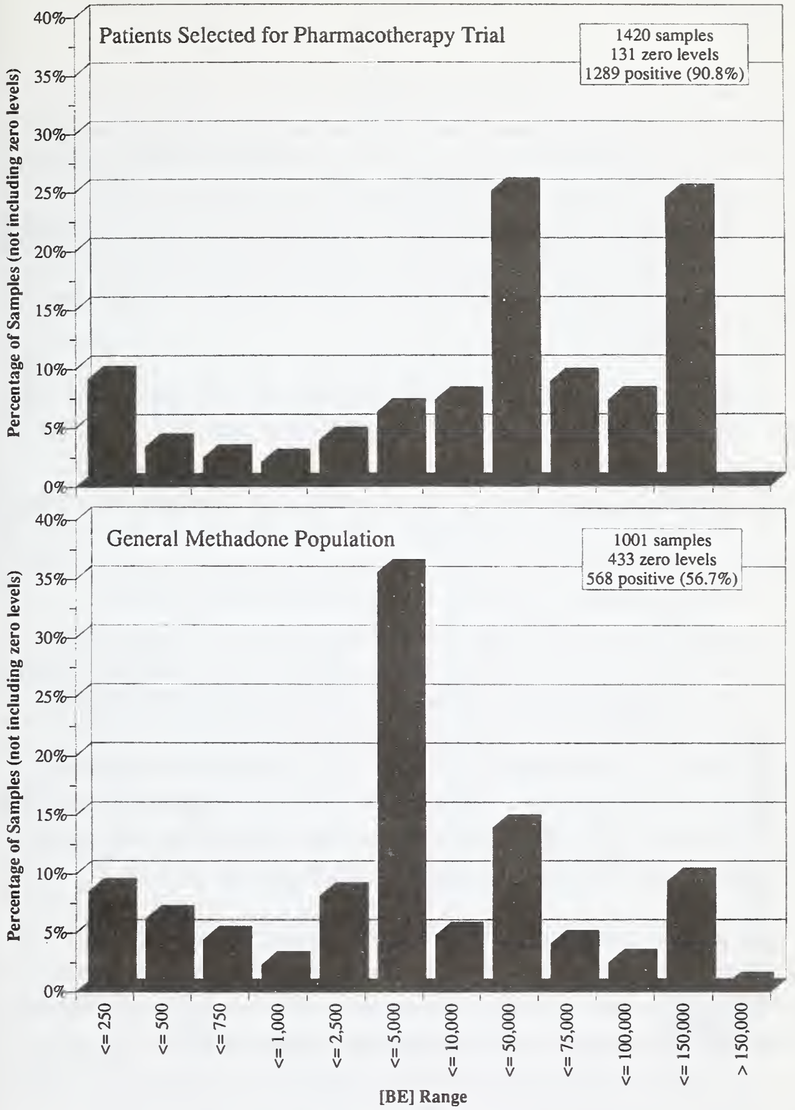

**FIGURE 6.** *Quantitative urine BE levels in two methadone maintenance populations: patients selected for a pharmacotherapy trial and general methadone patients. The incidence rate of urines positive for BE is 57% in the general methadone population positives compared to 91% in the pharmacotherapy population. BE levels in the general population are under 5,000 ng/mL 65% of the time, while 50% of the pharmacotherapy population has BE levels > 10,000 ng/mL and 25% between 100,000-150,000 ng/mL.*

physiological parameters including blood flow, urine flow, and body fluid pH.

Variability in the appearance of a substance abuse analyte is evident in serial urine samples collected from subjects who received intravenous cocaine (see figure 7) as part of a cardiovascular protocol (Nademanee et al. 1990). BE excretion varied despite the use of identical doses administered at the same time of day. It is noteworthy that this problem may be reduced by employing recently introduced algorithms that control for interindividual differences in BE excretion (Preston and Cone, this volume).

Caveats also apply to Cn adjustment of analyte levels. Extremely low or high Cn levels (e.g. < 0.1 or > 4.0) may produce spurious results. Each investigative group needs to define a range that avoids excessive adjustment with Cn, pending further research. In addition, all substance abuse analytes may not be appropriate for Cn adjustment. Alessio and colleagues (1985) have noted that not all environmental toxins parallel Cn in renal excretion. Similarly, additional data analysis from a pharmacotherapy-cocaine interaction safety study of 52 serial urines collected over 3 days of cocaine administration in four subjects (Haberny et al. 1995) suggests that not all urine substance abuse analyte levels parallel urine Cn levels. Pearson correlation coefficients of Cn and analyte urine levels demonstrate close correlations between Cn and amphetamine (0.95) and methamphetamine (0.91), a reduced correlation between Cn and BE (0.65), and even less of a correlation between Cn and ecgonine methyl-ester (0.48) and Cn and cocaine (0.35).

Thompson and colleagues (1990) have proposed a methodology to improve Cn adjustment in smoking cessation studies with potential applications to other substance abuse research. In a study of 279 male smokers, they demonstrated an increased correlation from 0.83 to 0.91 between urinary cotinine and plasma cotinine when the urine Cn value was modified according to a regression line of log-transformed, population-specific urine Cn levels. Alternatively, Simpson and associates (1993) have proposed a cost-saving procedure of limiting laboratory measures of Cn only when the urine color suggests dilution. They report that 96.5 percent of 516 samples were correctly identified by a visual inspection procedure, although the method has been criticized as being too subjective (Lafolie 1991). Li and colleagues (1996) performed a preliminary evaluation of various methods to adjust BE with urine Cn levels. This exercise has yet to identify a superior method, even when

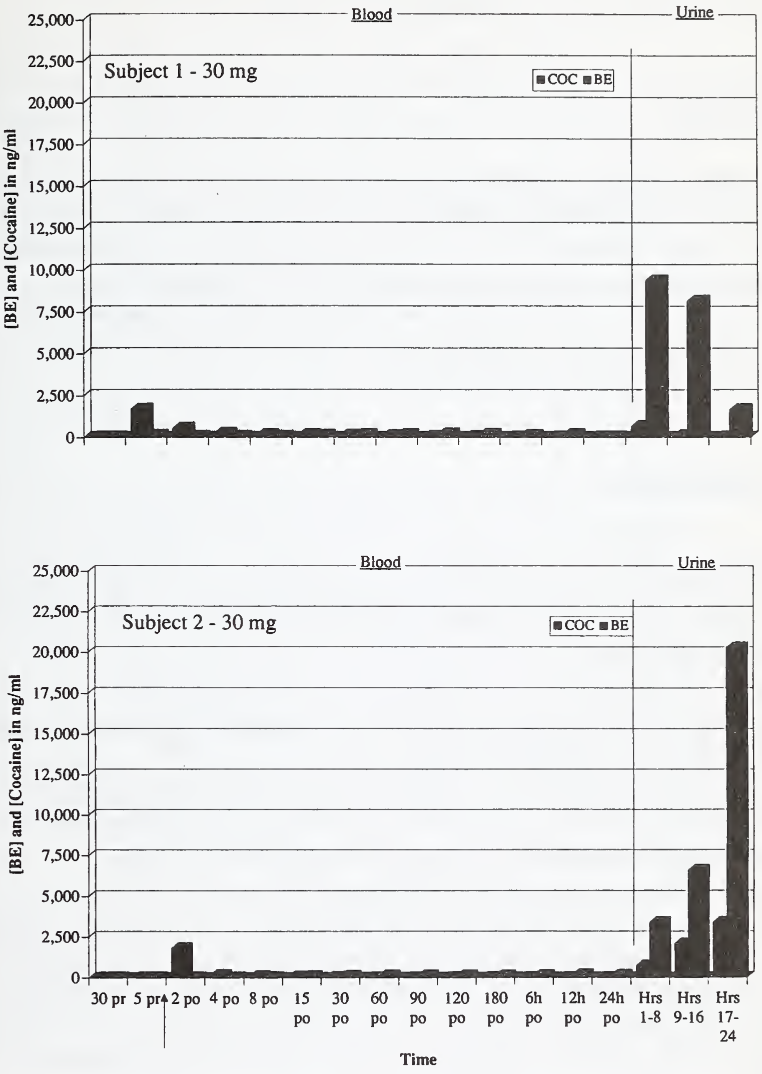

**FIGURE 7.** *Comparison of 24-hour monitoring of blood and urine following an IV bolus of 30 mg cocaine in two subjects. Interindividual differences in the timing of BE excretion kinetics across the three 8-hour urine collection periods are evident with quantitative urine BE levels decreasing in subject 1 and increasing in subject 2.*

employing the Thompson method. The effort is hampered by the lack of an obvious "gold standard" for comparison with quantitative urine levels (i.e., the kinetics of renal clearance differ from the kinetic processes producing blood, brain, and cerebrospinal fluid).

## SUMMARY

Used appropriately, quantitative levels can address research hypotheses and clinical issues that are otherwise untested by traditional qualitative urine results. Quantitative urine levels can provide new information in health services research, pharmacotherapy trials, studies of the interaction of cigarette smoking and substance abuse, additional studies of polysubstance abuse, and the linking of biological markers with phases of addiction and risk to relapse.

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# Use of Quantitative Urinalysis in Monitoring Cocaine Use

*Kenzie L. Preston, Kenneth Silverman, Charles R. Schuster, and Edward J. Cone*

## NEED FOR SENSITIVE MEASURES OF COCAINE USE

Cocaine use is a serious social and economic problem for which no solution currently exists. Considerable efforts have been expended to develop medications and other treatments for cocaine abuse, including clinical trials of a number of pharmacologic agents and behavioral approaches (Stitzer and Higgins 1995; Tutton and Crayton 1993). The primary goal of drug abuse treatment is to have patients decrease or stop their cocaine use. Because illicit drug use is a covert activity, it is usually measured indirectly through urine toxicology screens. Thus, urinalysis has become the primary outcome variable in most clinical trials of cocaine abuse treatments.

A major difficulty confronting drug abuse researchers is that appropriate pharmacological approaches to treatment are not clear. The exact basis for the rewarding effects of cocaine are not yet known, and although long-term neurochemical changes in cocaine abusers have been proposed, the exact nature of these changes have not been definitively identified (Cunningham et al. 1991; Johanson and Schuster 1995). Medications acting on different neurotransmitters (e.g., dopamine, serotonin, norepinephrine) through a variety of mechanisms (e.g., reuptake blockade, receptor antagonism, receptor agonism) have been evaluated (Tutton and Crayton 1993). The identification of medications with even partial efficacy could be valuable in guiding the direction of medication development activities. Therefore, the outcome measures used in the clinical trials in which experimental treatments are evaluated must be adequately sensitive to detect relatively small changes in cocaine use.

The most commonly used method for monitoring cocaine use in clinical trials is urinalysis. Typically, urine specimens are tested by qualitative immunoassays that detect benzoylecgonine (BE), the primary metabolite of cocaine. The standard cutoff concentration used in clinical trials to define positive and negative qualitative screens is 300 ng/mL of cocaine metabolite, the same requirement set in the Mandatory Guidelines for

Federal Workplace Drug Testing Programs (Department of Health and Human Services 1994). BE has a urinary excretion half-life of 6 to 8 hours (Ambre 1985) and can usually be detected in the urine for about 48 hours after cocaine administration (Saxon et al. 1988). The actual duration of detectability, however, is highly dependent on the amount of cocaine taken and individual rates of metabolism and excretion.

The persistence of cocaine metabolite in urine can lead to a phenomenon referred to as "carryover." Carryover occurs when a single episode of cocaine use results in multiple positive urine screens. This is particularly likely when specimens are collected frequently, at 48-hour intervals or less. When carryover occurs, it causes overestimation of the rate of cocaine use and, thus, may diminish the likelihood of detecting decreases in drug use in treatment studies. In addition, there is evidence to suggest that qualitative urinalysis is a relatively insensitive outcome measure. For example, significant decreases in self-reported cocaine use without concomitant significant decreases in rates of positive results from quantitative urinalysis has been found in a number of clinical trials (Covi et al. 1994; Kolar et al. 1992). Although the possibility of underreporting of cocaine use by cocaine users cannot be discounted (Magura et al. 1987; Sherman and Bigelow 1992), it is also possible that cocaine metabolite carryover obscures the true effects of treatment.

Another potential problem associated with urinalysis is the effect of fluid intake on BE concentration. Urine dilution can occur through normal variation in fluid consumption and excretion; however, deliberate dilution is known to occur, particularly when drug-positive urine specimens are linked to negative consequences. In fact, there are commercial products marketed for the purpose of defeating urine toxicology screen. Generally, the action of these products is based on urine dilution, encouraging the ingestion of large amounts of liquids. Unusually dilute specimens can be detected by measuring creatinine concentration and specific gravity. Guidelines recommended by the U.S. Department of Transportation for determination of abnormally dilute urine include a measurement of creatinine concentration of less than 20 mg/dL and a specific gravity of less than 1.003 (Goldberger et al. 1995).

Quantitative urinalysis may be a useful alternative to qualitative urinalysis as a primary outcome measure in clinical trials. This approach, coupled with creatinine concentrations, can be used to overcome problems of carryover and of urine dilution. Recently, the authors' laboratory examined BE and creatinine concentrations in urine specimens collected in a clinical trial of a behavioral treatment for cocaine abusers (Silverman et al. 1995, 1996) to determine the usefulness of quantitative urine testing. Criteria for estimating whether cocaine use has occurred during the interval between urine specimen collections have been developed (see table 1). These new use criteria could aid in the identification of urine specimens that are positive due to carryover and might improve the sensitivity of urinalysis for detecting decreases in cocaine use. This chapter presents information on the new use criteria and the application of those criteria to representative patients from the clinical trial.

## RULES FOR NEW USE CRITERIA

The new use criteria are based on assumptions about the pharmacokinetics of BE. As noted earlier, BE rapidly appears in urine after use, is excreted according to first-order kinetics, and has an average elimination half-life of 7.5 hours (Ambre 1985). Urine specimens that contain cocaine metabolite concentrations over 300 ng/mL, but that do not meet the new use criteria, are identified as positive specimens resulting from carryover from previous cocaine use. Urine specimens that contain cocaine metabolite concentrations less than 300 ng/mL and that do not meet the criteria were identified as negative. The new use criteria are summarized below.

**TABLE 1.** *Criteria for defining new use and carryover from quantitative urinalysis results.*

Assume new use if the sample meets any of the following criteria:

| | |
|---|---|
| RULE 1 | An increase in cocaine metabolite concentration to any value over 300 ng/mL compared to preceding urine specimen collected at interval of more than 48 hr |
| RULE 2A | Concentration decreased to less than one-half of concentration in preceding urine specimen collected at interval of more than 48 hr |
| RULE 2B | Concentration decreased to less than one-quarter of concentration in preceding urine specimen collected at interval of more than 48 hr |

**TABLE 1.** *Criteria for defining new use and carryover from quantitative urinalysis results (continued).*

| | |
|---|---|
| RULE 3 | Cocaine metabolite is greater than 300 ng/mL in the first urine specimen |
| RULE 4 | If the previous urine is missing (not collected), any urine specimen with cocaine metabolite greater than 300 ng/mL |
| RULE 5 | Creatinine less than 20 mg/dL (does not have to be positive for cocaine metabolite and cocaine metabolite/creatinine ratio) is increased compared to that of previous specimen |

## Rule 1

Assume new cocaine use occurred for a patient when: (a) the concentration of cocaine metabolite in the newly collected specimen exceeds the cutoff concentration for a positive specimen (300 ng/mL), and (b) the previous specimen (collected more than 48 hours ago) was negative (less than 300 ng/mL). This rule accounts for the appearance of a positive specimen when previous specimens tested negative and assumes that a new appearance of BE in the urine must result from a new use of cocaine.

## Rule 2A

Assume new cocaine use occurred for a patient when: (a) the concentration of cocaine metabolite in the newly collected specimen exceeds the cutoff concentration for a positive specimen (300 ng/mL), and (b) the concentration of cocaine metabolite in the newly collected specimen has not decreased by a factor of 2 (50 percent) below the concentration of the previous specimen (One-Half Rule).

## Rule 2B

Assume new cocaine use occurred for a patient when: (a) the concentration of cocaine metabolite in the newly collected specimen exceeds the cutoff concentration for a positive specimen (300 ng/mL), and (b) the concentration of cocaine metabolite in the newly collected specimen has not decreased by a factor of 4 (75 percent) below the concentration of the previous specimen (One-Quarter Rule).

Rules 2A and 2B assume that urine BE should be decreased by at least 50 percent or 75 percent, respectively, if no use of cocaine has occurred since the previous urine specimen collection at least 48 hours earlier. Two different criteria are being evaluated because of uncertainty about the exact amount of decrease expected under the natural conditions that exist in outpatient treatment research with patients who self-administer large and varying amounts of cocaine. Based on pharmacokinetic considerations of the excretion half-life of BE determined under laboratory conditions, these criteria are quite liberal. In fact, when a second specimen is obtained 48 hours following a positive specimen, the concentration of cocaine metabolite should be diminished to less than 2 percent of the original starting concentration, assuming a half-life of 8 hours. If the cocaine metabolite half-life is as long as 12 hours, then the concentration in the second specimen should have diminished to less than 10 percent of the original concentration. These liberal criteria were chosen because significant variability in the pharmacokinetics of cocaine and other factors can occur among individuals. An increase in BE concentration would also be counted as a new use under either Rule 2A or Rule 2B by the same rationale as given in Rule 1.

## Rules 3 and 4

Rules 3 and 4 were developed because of practical considerations in outpatient treatment trials. Rule 3—if the initial specimen is positive for cocaine metabolite, it is considered a new use. Rule 4—if a previous specimen is missing (not collected), the next collected specimen is considered a new use if it exceeds the cutoff concentration for a positive specimen (300 ng/mL). Rule 3 was adopted because of the lack of a previously collected comparison urine specimen for the first specimen collected in a trial. Rule 4 was needed because missed urine specimens are common in clinical trials. Under the conditions of the study in which these specimens were collected, a missed specimen would result in a 4- to 5-day interval between the previous specimen and the new specimen. As noted above for Rules 2A and 2B, it would be expected that the BE concentration would have decreased to below 300 ng/mL if no new cocaine use had occurred in that interval.

## Rule 5

Assume new cocaine use occurred for a patient when: (a) a dilute urine specimen, i.e., creatinine less than 20 mg/dL (does not have to be positive for cocaine metabolite) is obtained, and (b) the cocaine metabolite/creatinine ratio is greater than that of the previous specimen. This rule was developed for occasions when subjects attempt to subvert test results by ingestion of excess fluids.

## URINE BENZOYLECGONINE AND CREATININE CONCENTRATIONS IN URINE SPECIMENS OF PATIENTS IN CLINICAL TRIALS

Urine specimens from a clinical trial were used to evaluate the potential utility of the new use criteria. Specimens had been collected three times per week for up to 17 weeks in methadone maintenance patients participating in a clinical trial of a behavioral treatment for cocaine abuse (Silverman et al. 1996). The behavioral treatment was based on an abstinence reinforcement model in which patients earned vouchers exchangeable for goods and services for each cocaine-negative urine specimen. Assays for the cocaine metabolite (BE) concentrations were performed with TDx® Cocaine Metabolite Assay reagents (TDx) (Abbott Laboratories, Abbott Park, IL) on a TDx instrument according to manufacturer's recommended procedures. The cross-reactivity of this assay for BE was 100 percent and less than 1 percent for cocaine, ecgonine methyl ester, and ecgonine. The lower limit of sensitivity of the assay for cocaine metabolite was 30 ng/mL. Specimens that contained concentrations of cocaine metabolite greater than 5,000 ng/mL were diluted with TDx reagent buffer and reanalyzed with the appropriate control samples. Creatinine measurements were performed by the Jaffe method with Boehringer Mannheim Diagnostic reagents on a Hitachi 704 analyzer (Boehringer Mannheim, Indianapolis, IN).

Visual inspection of graphs of urine BE concentrations from individual subjects suggested that most participants used cocaine intermittently, with cyclical patterns of high and low BE concentrations. BE concentrations from a representative subject are shown in figure 1 on a log scale. Concentrations greater than 300 ng/mL are indicated by circles, and concentrations less than 300 ng/mL are indicated by triangles. Horizontal lines indicate the cutoff for the qualitative testing (300 ng/mL) and the limit of detection for the assay (LOD; 30 ng/mL). This subject participated for a period of approximately 13 weeks, during which there were a total of 40 urine collections. The individual missed two urine collections, days 34 and 37, indicated by dashed lines on the figure. BE equivalent concentrations varied over a wide range, from below 30 to 86,700 ng/mL.

Of the 38 specimens collected, 34 were considered positive (greater than 300 ng/mL), and 4 were negative (less than 300 ng/mL).

Application of the new use criteria to the urine BE concentrations identified 11 of the 34 (32 percent) positive urine specimens as possible cases of carryover by the One-Half Rule (Rule 2A), indicated on the figure as open circles. When the new use criteria were applied using the more stringent One-Quarter Rule (2B), two fewer specimens were identified as carryover, specimens 13 and 15. The new use criteria consistently identified as carryover those specimens in which there were substantial decreases in concentration compared to the prior specimen, but not to below the 300 ng/mL cutoff. Thus, these cases appear to be due to carryover rather than to a new use of cocaine between two consecutive urine specimen collections.

There were two samples, 35 and 38, that were identified as new uses via Rule 4, the Missing Specimen Rule. If the missing specimens (34 and 37) had been ignored, and the concentration compared to the next previous specimens (33 and 36), both specimens would have been identified as carryover positives by the One-Half Rule (2A), but as new uses by the One-Quarter Rule (2B). Given the circumstances (missed clinic visits) and the continued presence of BE at concentrations well above the 300 ng/mL level, these BE concentrations are very likely to be due to cocaine use that occurred after collections of specimens 34 and 37.

Rule 5 was designed to adjust for dilute urine specimens. Adulteration by dilution was relatively rare in the clinical trial in spite of the fact that subjects in the experimental group could earn vouchers for being cocaine abstinent and, thus, had a relatively strong incentive for having cocaine-negative specimens. No specimens with creatinine concentrations below the 20 mg/dL were found in the subject whose data are shown in figure 1; however, some cases of suspected urine dilution were found in other subjects. BE and creatinine concentrations for one such individual with multiple dilute urine specimens are shown in figure 2. This participant was among the group of subjects who could earn vouchers for cocaine-negative urine specimens. Drug use was monitored in urine specimens throughout the study. Test results had no programmed consequence in specimens 1 through 15; vouchers became available to subjects beginning with the 16th specimen. This subject had three urine specimens with creatinine concentrations at or below 20 mg/dL, the cutoff for dilute urine. Two of those specimens (22 and 23) coincided with BE concentrations below 300 ng/mL. The BE/creatinine ratios were increased relative to

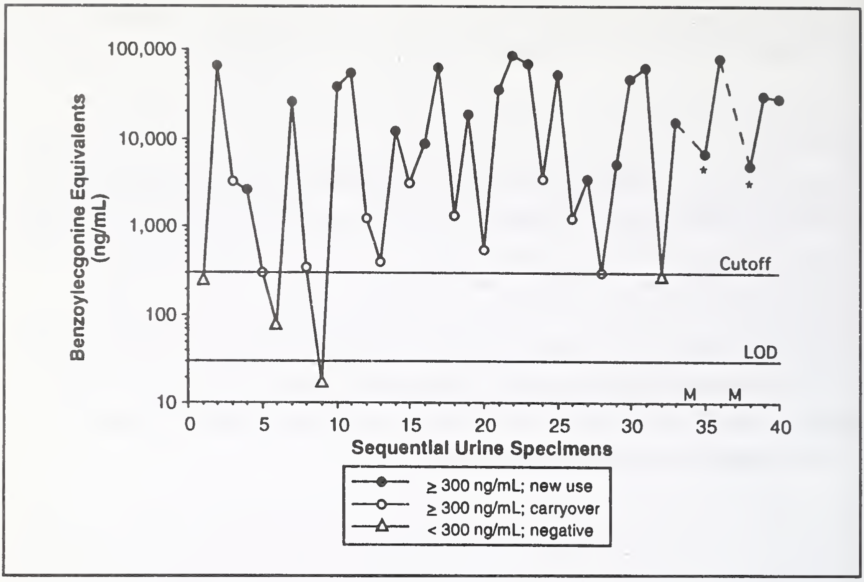

**FIGURE 1.** *Quantitative urinalysis results of sequential urine specimens of a subject in a cocaine abuse treatment clinical trial. M indicates missing specimens.*

the previous urine specimens and, thus, met the criteria as new uses as outlined in Rule 5. The suggestion that the subject used cocaine during this period is supported by the fact that five consecutive specimens (19 through 23) all contained BE concentrations around 200 ng/mL, below the 300 ng/mL cutoff but well above the limit of detection of the assay. Based on the known pharmacokinetic profile of excretion of cocaine and BE, it is extremely unlikely that BE concentrations would remain in the 200 ng/mL range over a period of several days without use. Data from other subjects indicate that when cocaine use is completely stopped, concentrations fall to below the limit of detection within several days.

## CONCLUSION

There is growing interest in the use of quantitative urine testing in clinical trials. Changes in the pattern, frequency, and amount of use that are not apparent from qualitative urinalysis are discernible from quantitative urinalysis. Overestimation of drug use from carryover also can be avoided by the development of criteria (such as the new use

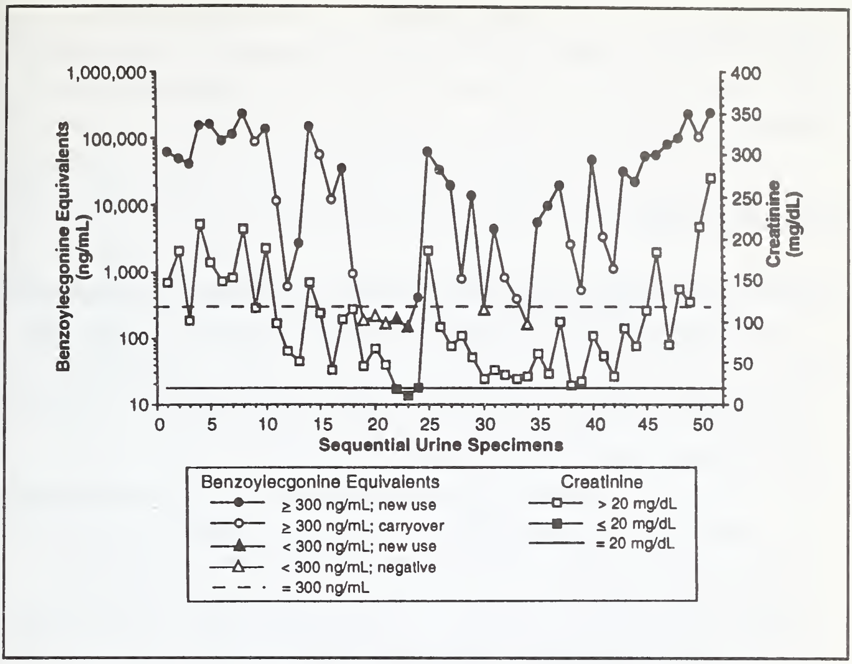

**FIGURE 2.** *Benzoylecgonine and creatinine concentrations in sequential urine specimens of a representative subject from a cocaine abuse treatment clinical trial.*

criteria described here) that are based on the pharmacokinetic profile of cocaine and its metabolites. These criteria can be applied objectively and consistently. However, quantitative urine testing is more expensive than qualitative testing, and urine drug/metabolite concentration can be affected by many variables such as the time between drug use and urine collection, fluid intake, and interindividual metabolic differences. For example, a urine specimen collected several days after self-administration of a large amount of drug could have the same drug/metabolite concentration as a specimen collected just after self-administration of a small amount of drug. Thus, the time of specimen collection could have greater impact on concentration than the total amount of drug used. Fluid intake is sometimes used by subjects to alter urine drug/metabolite concentration. As found in the present study, however, corrections can be made using a biological indicator such as creatinine to adjust for water consumption. Few clinical trials have been conducted with quantitative testing, though at least one study suggests that quantitative testing may be more sensitive to decreases in drug use than qualitative tests (Batki et al. 1993). McCarthy (1994) has also reported on the utility of quantitative urine drug testing in the context of substance abuse treatment. Future studies will be needed to determine the true conditions under which quantitative analysis of drugs in urine is useful and cost effective.

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# Is Quantitative Urinalysis More Sensitive?*

*Shou-Hua Li, Nora Chiang, Betty Tai, Charles K. Marschke, and Richard L. Hawks*

Outcome measures for assessing clinical efficacy of cocaine addiction pharmacotherapy should reliably and accurately reflect the benefits of the treatment. A core battery of outcome measures has been proposed by the Food and Drug Administration (FDA) and used by investigators for such trials. These measures include: (1) cocaine use by urinalysis, self-report, or both; (2) retention in treatment; (3) patient self-assessment; and (4) physician global assessment. Currently, urinalysis is the only generally accepted surrogate biological marker for objectively monitoring cocaine intake.

Cocaine is eliminated from the body primarily by metabolism and has an elimination half-life of approximately 1 to 1.5 hours (Cook et al. 1985; Jones 1984). Benzoylecgonine (BE) is a major metabolite of cocaine. Approximately 30 to 50 percent of the dose of cocaine is excreted in the urine as BE, whereas only 2 to 3 percent is excreted in the urine as unchanged cocaine (Ambre 1985; Cook et al. 1985; Hamilton et al. 1977). The elimination half-life for BE of 7 hours is much longer than that for cocaine; BE can be detected in the urine for 2 days or longer after a single dose of cocaine (Reid et al. 1995). Therefore, BE is the most commonly screened target for assessment of cocaine use. In general, urinary BE concentrations are highly variable and depend on dose and route of administration, pharmacokinetics for each individual, urine volume, and factors such as disease state and drug interactions that may affect the pharmacokinetics.

Qualitative urinalysis has been widely employed for detecting illicit drug use in the workplace (Hawks and Chiang 1986). Immunoassays such as radioimmunoassay (RIA), enzyme immunoassay (EIA), and fluorescence polarization immunoassay (FPIA) are the most commonly used methods for detecting BE in the urine. A BE concentration of 300 ng/mL has been typically established as the cutoff point. Any concentration below the

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level of 300 ng/mL is considered a negative sample (a clean urine), any sample that has a BE concentration above 300 ng/mL is a positive sample (a dirty urine). This approach provides binary data (clean or dirty).

Recently, there has been increased interest in the use of quantitative urinalysis as an outcome measure in clinical trials. Instead of urine samples being assessed in a binary fashion, data can be evaluated quantitatively to assess an increase or reduction in urinary BE concentrations. Batki and colleagues (1993), studying the effect of fluoxetine on cocaine use, showed that qualitative urinalysis did not reveal a statistically significant difference between the treatment and control groups, whereas quantitative urinalysis did.

Chromatography assays such as gas chromatography/mass spectrometry (GC/MS) provide a precise estimate of BE concentration. However, the high cost of these assays could limit their utility in clinical trials where a large number of urine samples are collected. Immunoassay methods, such as FPIA and EIA, can provide a quantitative estimate of urinary BE concentrations (Crosby et al. 1991). The quantitative immunoassay is inexpensive compared with the chromatographic method, although it is still more costly than qualitative urinalysis. The recent development of quantitative techniques for automated mass screening using immunoassays has made this approach feasible for use in clinical trials (Foltz et al., this volume).

This study uses simulated BE data from a set of simple clinical models to evaluate whether quantitative urinalysis is a more sensitive measure of the reduction in frequency or amount of cocaine use than is qualitative urinalysis. The model defined a treatment effect as a 60 percent reduction in cocaine use—either in daily amount or weekly frequency (at the same daily amount). A 60 percent reduction in cocaine use was considered to be clinically significant (Tai 1993). In addition, comparison was made of urine sampling schemes of three times per week and once per week for assessing treatment outcomes.

## METHODS

### Pharmacokinetic Model

Cocaine disposition can be described by a one-compartment model as depicted in figure 1 (Ambre 1985). The pharmacokinetic parameters

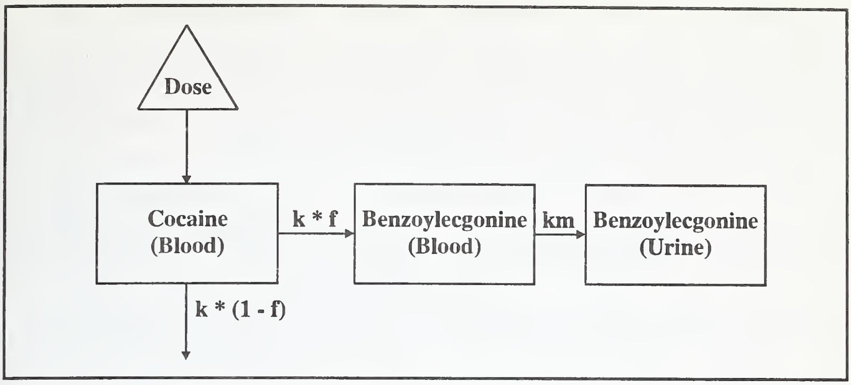

**FIGURE 1.** *Pharmacokinetic model for cocaine disposition.*

KEY: k = overall elimination rate constant for cocaine
f = fraction of cocaine dose metabolized to benzoylecgonine
k*f = rate constant for the formation of benzoylecgonine
km = urinary excretion rate constant for benzoylecgonine
k* (1 - f) = rate constant for the elimination of cocaine by routes other than metabolism to benzoylecgonine

used in this simulation were obtained from a clinical pharmacokinetic study involving 10 subjects (Jones 1992). The averages of the overall elimination rate constant for cocaine (k), the urinary excretion rate constant for BE (km), and the fraction of cocaine dose metabolized to BE (f) were 0.44 $hr^{-1}$, 0.097 $hr^{-1}$, and 30 percent, respectively, and the standard deviations were 0.074 $hr^{-1}$, 0.020 $hr^{-1}$, and 7.2 percent, respectively. The parameters of k and km are in good agreement with those reported by Ambre (1985) and the parameter f is in good agreement with recent reports of f values equal to 0.22 and 0.36 by Ambre and colleagues (1988) and Jeffcoat and colleagues (1989), respectively. The individual subjects' pharmaco-kinetic parameters for the simulation were randomly generated, assuming normal distribution, so that the mean and standard deviation of the simulated group parameters matched those calculated from the clinical pharmacokinetic study.

## Assumptions

The model assumed that there were no intrasubject variations in pharmacokinetic parameters or in urine volumes and that self-administration was by the intravenous (IV) route. The urine flow rate was taken as 1 mL/min (0.06 L/hr). Urinary BE concentrations were calculated for a 9:00 a.m. sample for Monday, Wednesday, and Friday. Self-dosing times were randomly assigned from 6:00 a.m. to 12 midnight throughout the study. The following equation was used to describe the urinary BE concentrations at time *t* (see the Appendix):

$$\boxed{(\mathrm{BE})t = \frac{(k*f*\mathrm{dose})*(km*e^{-(k*t)}*(e^{k}-e^{(-k)})-k*e^{-(km*t)}*(e^{km}-e^{(-km)}))}{k*(km-k)*(0.06*2)}}$$

## Simulation

Three groups of urinary BE concentrations were simulated to mimic a 12-week clinical study. Each group consisted of data from a simulation with a sample size of 30 where the IV dose of 200 mg/day was given for 7 days a week before the treatment period. Group A served as a control or placebo group and groups B and C were treatment groups. In group B, it was assumed that treatment resulted in a reduction in the daily amount of cocaine use with no change in the frequency. In group C, it was assumed that treatment resulted in a reduction in the weekly frequency of use with no change in the daily amount. A treatment effect (reduced cocaine use) was assumed to start during week 2 and continue through week 5, after which no further reduction would occur through week 12. The extent of the daily dose reduction for group B was assumed to be linear and at a rate of 15 percent per week; this reduction was equivalent to a 1 day/week reduction for group C. Overall, this treatment assumption resulted in an approximately 60 percent decrease in cocaine use for both groups. The specific weekdays of cocaine use from weeks 2 to 12 were assigned randomly for group C. Table 1 presents these dosing assumptions.

## Statistical Analysis

Because a 60 percent reduction in cocaine use was considered to be clinically significant, it was necessary to establish statistically that this degree of reduction could be detected in urine. The approach taken was to assume a reduction in four increments of 15 percent each over 4 weeks to achieve the 60 percent level and to analyze the simulated urine concentrations at each increment to be sure that the reduction could be detected at or before the 60 percent point. A simple *t* test was used to test the difference between each treatment group (group B or group C) and

**TABLE 1.** *Assumed daily cocaine consumption as altered by treatment.*

| Weeks | 1 | 2 | 3 | 4 | 5 to 12 |
|---|---|---|---|---|---|
| Control (A) | | | | | |
| Daily dose (mg) | 200 | 200 | 200 | 200 | 200 |
| Frequency (days/week) | 7 | 7 | 7 | 7 | 7 |
| Treatment effects | | | | | |
| % Reduction of weekly dose | 0 | 15 | 30 | 45 | 60 |
| Reduction in daily amount (B) | | | | | |
| Daily dose (mg) | 200 | 170 | 140 | 110 | 80 |
| Frequency (days/week) | 7 | 7 | 7 | 7 | 7 |
| Reduction in frequency (C) | | | | | |
| Daily dose (mg) | 200 | 200 | 200 | 200 | 200 |
| Frequency (days/week) | 7 | 6 | 5 | 4 | 3 |

the placebo group (group A) in the quantitative urinalysis scenario for each week. A chi-square test was used to test the difference between each treatment group and the placebo group in the qualitative urinalysis scenario for each week.

## RESULTS

### Comparison of Simulated Data and Clinical Data

Urine BE concentration simulated for a representative of group C is presented in figure 2. The variability of the BE concentrations is seen to increase significantly when the frequency of cocaine use decreased starting in week 3. When cocaine use was reduced to 3 days per week (weeks 5 to 12), the BE concentration fell below the cutoff concentration in several samples but rebounded to concentrations three orders of magnitude higher in the subsequent samples. These results are similar to the large variations reported in clinical studies (Batki et al. 1994; Crosby et al. 1991).

Table 2 presents a comparison of the BE data generated from the simulation model with the baseline data for 50 cocaine abusers who were methadone patients participating in a clinical trial to evaluate fluoxetine

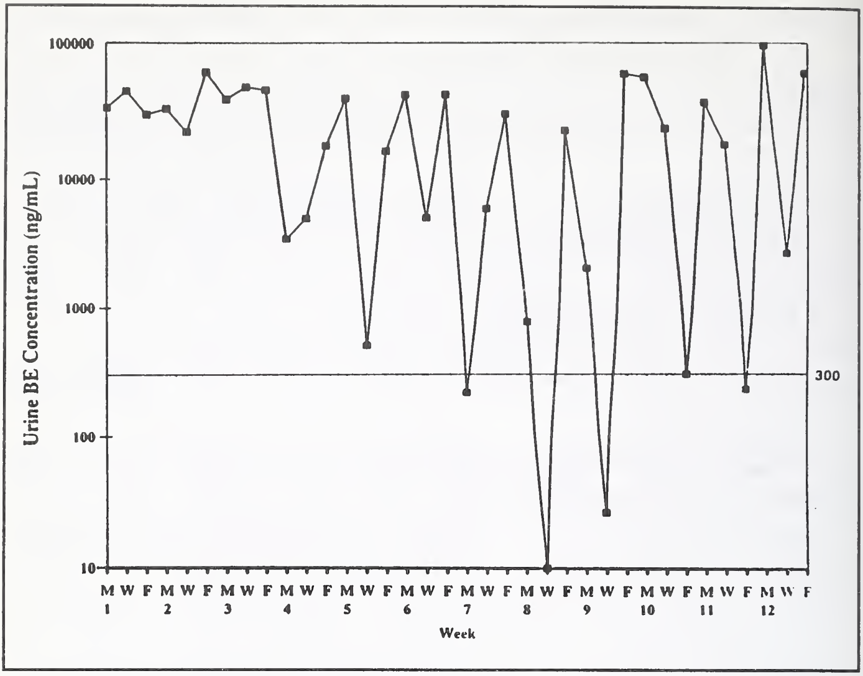

**FIGURE 2.** *Urine benzoylecgonine concentrations simulated for a representative of group C.*

for treating cocaine addiction (Batki et al. 1994). The cocaine usage pattern, based on self-reports by the 50 subjects before the trial started, showed an average frequency of cocaine use of 4.8 days/week. BE urine concentrations were simulated for two 50-subject groups using the proposed pharmacokinetic model, but with different dosage regimens. An IV usage pattern of 200 mg/day, 7 days/week was assumed for the first group (as in the placebo group A of the comparison simulations). The second group was assumed to ascribe to the same weekly usage pattern as reported for the clinical trial but at an IV dose of 600 mg/day.

There was a wide distribution of BE concentrations for the clinical data, with most subjects tending toward high BE concentrations between 10,000 and 1,000,000 ng/mL. The distribution of BE for group A (control) was very narrow (10,001 to 100,000 ng/mL). When a frequency of use the same as that for the clinical data was assumed and the daily dose increased to 600 mg, the BE distribution for these simulated data was similar to the clinical data.

**TABLE 2.** *Urinary benzoylecgonine concentrations for simulated and clinical data (sample size = 50).*

| Urine BE concentrations (ng/mL) | 0-300 | 301-1,000 | 1,001-10,000 | 10,001-100,000 | 100,001-1,000,000 |
|---|---|---|---|---|---|
| Clinical data* | 4 | 5 | 7 | 19 | 15 |
| Simulated data based on 200 mg daily use | 0 | 0 | 4 | 46 | 0 |
| Simulated data based on 600 mg and Batki's self-report pattern | 4 | 1 | 7 | 25 | 13 |

KEY: * = Clinical data provided by Batki et al. (1994) with the following frequency of use pattern from self-report.

| Days/week of cocaine use | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| # of subjects | 1 | 3 | 3 | 7 | 7 | 6 | 6 | 17 |

The mean and standard deviation of the clinical data (86,000±118,000 ng/mL) was much larger than for the simulated control group (32,000 ± 16,000 ng/mL) but closer to those for the simulated data (74,000±78,000 ng/mL) using a larger dose and the same usage pattern of the clinical data. The coefficient of variation for the clinical data (137 percent) was slightly larger than that for the simulated data (105 percent) in the second case. This variance might be expected because the subjects in the clinical trial would likely use various amounts of cocaine and routes of administration. The similar mean and similar pattern of BE distribution for the simulated and clinical data support the assumption that the pharmacokinetic model is valid.

## Quantitative Urinalysis

Table 3 presents the weekly group mean and the standard error for urinary BE concentrations for a urine sampling schedule of three times

**TABLE 3.** *Weekly group mean for urine benzoylecgonine concentration simulated for three times per week sampling.*

| Week | Control Group (A) | Reduction in Daily Amount (B) | Reduction in Frequency (C) |
|---|---|---|---|
| 1 | 31,984<br>(2165)* | 32,079<br>(2031) | 29,738<br>(2238) |
| 2 | 26,944<br>(2180) | 28,832<br>(1844) | 29,596<br>(1924) |
| 3 | 29,510<br>(2477) | 25,620<br>(1739) | 25,193<br>(3004) |
| 4 | 30,514<br>(2051) | 18,002**<br>(1095) | 21,346**<br>(2161) |
| 5 | 37,342<br>(2719) | 14,199**<br>(957) | 16,131**<br>(1914) |
| 6 | 34,592<br>(2850) | 13,691**<br>(1186) | 11,308**<br>(1157) |
| 7 | 37,633<br>(3199) | 13,134**<br>(883) | 15,092**<br>(1828) |
| 8 | 33,783<br>(2062) | 13,970**<br>(1408) | 15,666**<br>(2479) |
| 9 | 31,944<br>(2371) | 14,622**<br>(1153) | 20,373**<br>(2309) |
| 10 | 35,121<br>(2756) | 14,360**<br>(954) | 12,649**<br>(1722) |
| 11 | 30,753<br>(2313) | 12,614**<br>(983) | 15,071**<br>(2144) |
| 12 | 30,591<br>(2458) | 11,704**<br>(796) | 17,320**<br>(2004) |

KEY: * = Standard error; ** = significantly different from group A, $p < 0.05$.

per week. The simulated BE values for each week were determined as the mean of the BE concentrations on Monday, Wednesday, and Friday for the week. A statistically significant difference ($p < 0.05$) was shown between the control group and the treatment groups in week 4 when a 45 percent reduction in the weekly dose was reached—in daily amount of cocaine used (group B) or in frequency of use (from 7 days to 4 days per week, group C). The weekly mean for BE concentrations was similar for groups B and C. The standard errors for group C were about twice those for group B when the reduction in the weekly dose reached 30 percent (at week 3). This reduction is a result of the large fluctuation resulting from the variations in the interval between dosing and sampling.

Table 4 presents the weekly data for urinary BE concentrations for a sampling schedule of once a week. The Monday samples were used. The weekly means for group B were similar to those for group C, whereas the standard errors for group B were smaller than those for group C. A statistically significant difference could be detected between either treatment group (group B or group C) and the control group (group A) when there was a 60 percent reduction in the weekly dose (week 5). The statistical difference was observed for every week from weeks 5 to 12 of group B. However, group C failed to show a statistical difference for weeks 9 and 12 even though the reduction had occurred from week 5 on as a result of the large variability for the BE data for group C.

When the data for the two sampling schedules (one time and three times per week) were compared, the means for each corresponding group were similar, but the standard errors for one time per week sampling were much larger than those for the three times per week sampling (figures 3 and 4). A further reduction in cocaine use of 15 percent (from 45 percent to 60 percent or fourth week to fifth in the figures) was required to detect the statistical difference for the one time per week sampling because of the large variations of the weekly BE concentrations associated with one time per week sampling. The weekly mean of three samples would smooth out these variations. The reduction in daily amount of cocaine use curve (figure 3) had a smoother curve than the reduction in frequency curve (figure 4) after week 5.

## Qualitative Urinalysis

Figure 5 presents the weekly percentage of positive (dirty) urine samples for the three times per week urine collection schedule using the “majority rule” analysis. This analysis, widely used in clinic trials, assumes the weekly urine is dirty if at least two of the three samples for the week are positive. Group A (control) and group B (reduction in amount) always presented 100 percent positive samples with no significant difference (chi-square test) between them. However, a significant difference was observed between groups C and A for 5 of the 8 weeks when the

**TABLE 4.** *Weekly group mean for urine benzoylecgonine concentration simulated for once a week sampling.*

| Week | Control Group (A) | Reduction in Daily Amount (B) | Reduction in Frequency (C) |
|---|---|---|---|
| 1 | 33,814<br>(3162)* | 37,674<br>(3745) | 29,566<br>(3404) |
| 2 | 28,414<br>(4325) | 31,753<br>(3012) | 32,373<br>(2872) |
| 3 | 33,231<br>(4438) | 29,613<br>(3014) | 28,256<br>(4785) |
| 4 | 31,204<br>(3910) | 21,684<br>(1985) | 24,525<br>(3587) |
| 5 | 37,768<br>(5637) | 16,929**<br>(1758) | 19,684**<br>(3560) |
| 6 | 36,626<br>(4967) | 13,569**<br>(1729) | 8946**<br>(2277) |
| 7 | 31,270<br>(4013) | 13,692**<br>(1334) | 10,183**<br>(2432) |
| 8 | 32,969<br>(3725) | 15,738**<br>(2103) | 14,460**<br>(4004) |
| 9 | 32,440<br>(4293) | 15,419**<br>(1996) | 23,818<br>(4061) |
| 10 | 36,516<br>(4391) | 17,931**<br>(1723) | 9755**<br>(2313) |
| 11 | 27,696<br>(2684) | 13,566**<br>(1581) | 16,307**<br>(2907) |
| 12 | 27,805<br>(2904) | 9432**<br>(867) | 18,766<br>(4057) |

KEY: * = Standard error; ** = significant different from group A,. $p < 0.05$.

frequency of use of group C was reduced to three times per week (weeks 5 to 12).

Because groups A and B presented 100 percent positive samples all the times, neither a thrice-weekly nor a once-weekly sampling schedule for

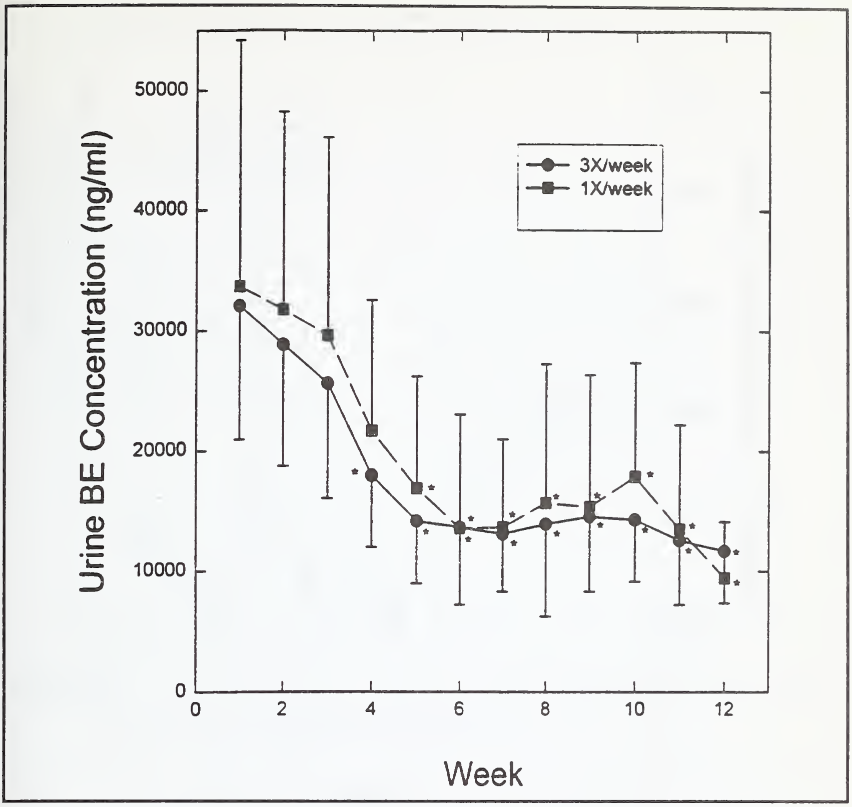

**FIGURE 3.** *A comparison of weekly quantitative urinalysis (mean and standard error) simulated between three times per week versus one time per week sampling for reduction in daily amount group (group B).*

KEY: * = Significantly different from control group, $p < 0.05$.

qualitative urinalysis could detect the difference in the amount of daily dose between these two groups.

Figure 6 compares the percentage of positive (dirty) urine samples for group A and group C using (1) the one time a week sampling schedule, (2) the three times per week schedule using the majority rule analysis, and (3) the three times per week schedule using the actual percentage of positive urine samples. Group A presented 100 percent positive urines at all times. For group C, the data using the majority rule for the three times

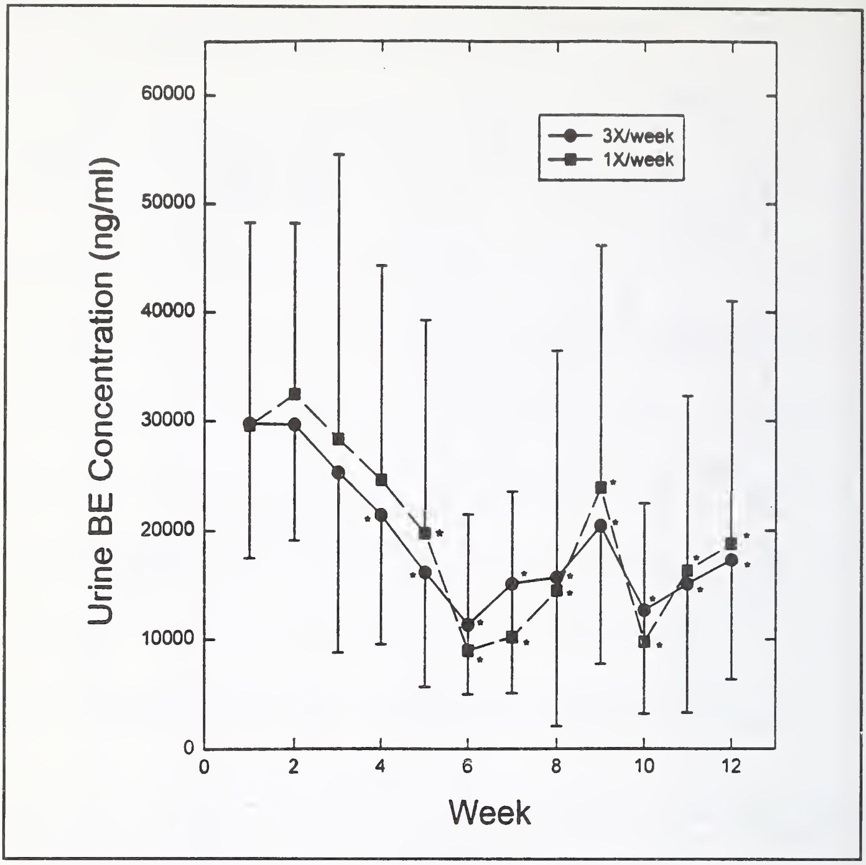

**FIGURE 4.** *A comparison of weekly simulated quantitative urinalysis (mean and standard error) between three times a week versus one time per week sampling for reduction in frequency group (group C).*

KEY: * = Significantly different from control group, $p < 0.05$.

per week schedule always gave the highest estimates for the percentage of positive urines, higher than did the actual percentage of positive samples. The one time per week sampling could give either higher or lower estimates than the actual percentage of dirty urines. When the frequency of use was reduced to three times per week (week 5), a significant difference was detected between the treatment (group C) and control (group A) groups for all the remaining 8 weeks using the actual data for three times per week sampling. Group C differed significantly from

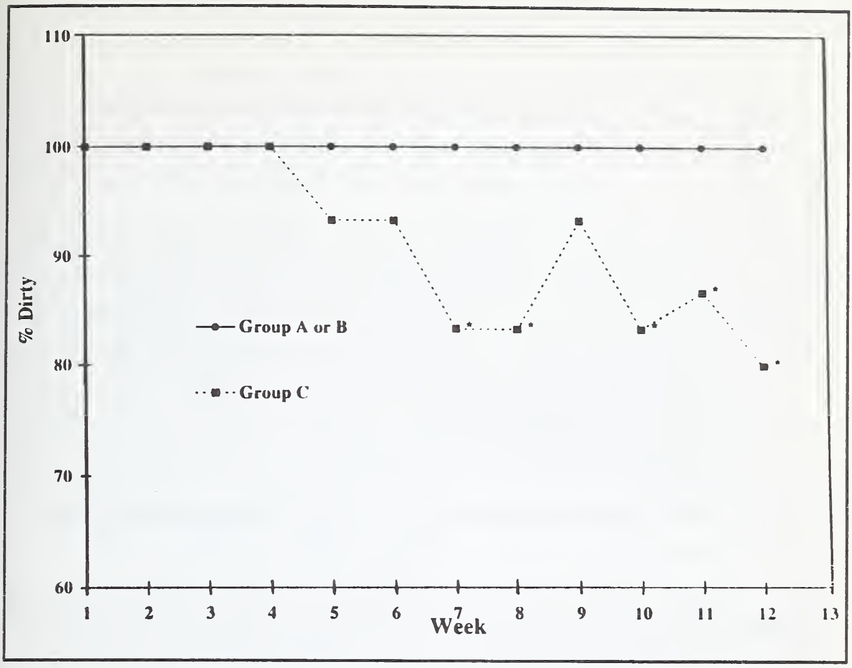

**FIGURE 5.** *Weekly percentage of dirty urine simulated for three times per week sampling schedule.*

KEY: * = Significantly different from group A, $p < 0.05$.

group A in 6 of 8 weeks when one time per week sampling was simulated. This difference was reduced to 5 of 8 weeks when the majority rule analysis was used for the three times per week schedule.

## DISCUSSION

Urinary data in general are not a very sensitive marker for the assessment of cocaine use and vary widely because of the differences in the amount of cocaine used, the frequency of use, the route of administration (intranasal, oral, or smoking), the urine volume (urine flow rate), sampling times, and factors such as disease state and concomitant medications. In addition, there are intraindividual differences in these parameters from day to day. It is difficult to use urine data to estimate the frequency and amount of cocaine use. Depending on the frequency of urine sampling and the pattern of cocaine use (daily versus binge use), a

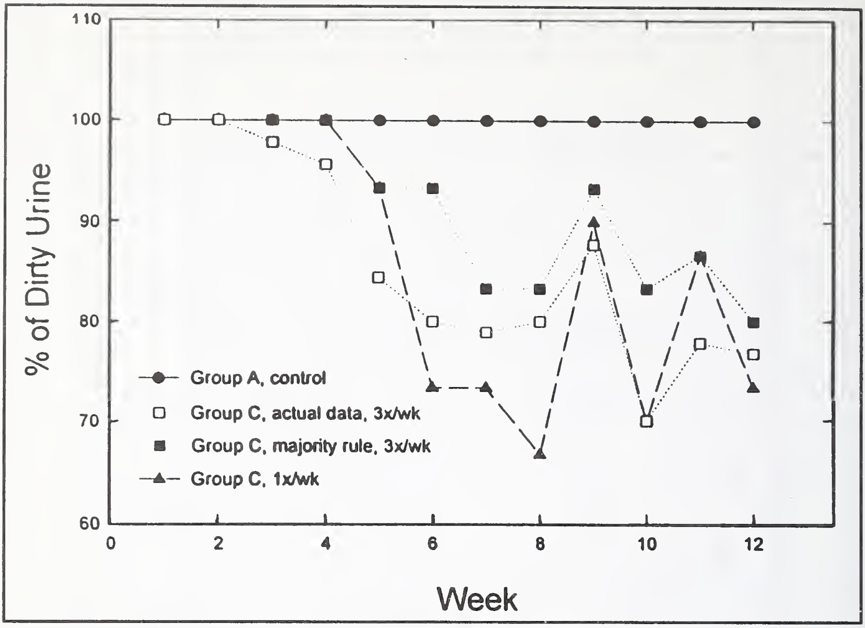

**FIGURE 6.** *A comparison of weekly percentage of dirty urine data simulated between three times per week versus. One time per week sampling schedule.*

KEY: * = Significantly different from group A, $p < 0.05$.

negative urine sample may not indicate a lack of cocaine use, and a positive urine sample may reflect the carryover effects of an episode several days before sampling.

Cocaine is usually administered by an intranasal, IV, or smoked route of administration. The absorption is different for the different routes of administration, which results in different urinary excretion profiles after a single dose (Cook et al. 1985; Jeffcoat et al. 1989; Jones 1984; Jones, this volume). Intranasal absorption is slow and the bioavailability is approximately 40 to 80 percent. Smoking provides a rapid absorption but low bioavailability (approximately 20 to 45 percent). The pharmacokinetic profile for smoking is similar to that for IV administration, but a much larger dose is required to achieve the same plasma and urine concentrations. Because of the wide range of street doses a subject may have used as well as the uncertainty of when the dose was taken, similar urinary BE concentrations were observed for cocaine addicts following different routes of administration. Because the IV dose provides a simple pharmacokinetic model, it was chosen for the simulation. A dose of 200 mg was used because the pharmacokinetic parameters were derived from a clinical pharmacokinetics study using this dose. In addition, the urinary BE after this dose can be detected (using the 300 ng/mL cutoff) for 2 to 3 days, which is consistent with the report that the detection window for BE is 1 to 2 days after a regular cocaine dose.

These simulated data were based on a simple clinical situation with an ideal homogeneous patient population with the same usage pattern, dose, and route of administration. The only variables were the dosing times and individual pharmacokinetic parameters. In actual clinical settings, urinary BE concentrations are more variable, as noted in the Results section in which a coefficient of variation calculated for actual clinical data (137 percent) was much larger than that for the two simulated cases (105 percent and 50 percent). Because the number of subjects required to detect a specified reduction in cocaine use depends on the variability of the BE concentrations, a sample size of 30 for each group would be too small to detect any difference between the treatment and the control groups in actual clinical situations. Based on the BE concentrations in the clinical data of Batki and colleagues (1993), the number of subjects required to detect a 60 percent reduction in cocaine use at a significance level of 0.05 and with a power of 80 percent would be 90 subjects per group. If a power of 95 percent is required, the number of subjects would have to increase to 140 per group. It should be noted that these estimates of group size are based on this single clinical data set (that of Batki et al.)—the only one available to the authors.

Two hypothetical situations were used to compare the treatment effects: a change in daily amount of use and a change in frequency of use. All the individuals were assumed to be equally affected by the treatment. In an actual situation, the treatment group would be a mixture of subjects, some of whom would manifest a reduction in amount used, some in frequency, and others showing no change in habits. The magnitude of the individual reductions and the time required to reach and maintain those concentrations would be expected to be variable across subjects and to further complicate the detection of treatment outcome. For instance, if a treatment has a significant effect on a small segment of the group leading perhaps to cessation of use, an analysis based on the average across the group might not be able to detect any significant difference from the control group, but an obvious subgroup might emerge if the analysis includes an assessment of consecutive negative urine days or weeks.

For this simulation, qualitative urinalysis could not detect a reduction in the amount of daily dose for daily users but could detect a reduction in the frequency of cocaine use from 7 to 3 days per week. Urinary BE concentration depends on dose, route of administration, pharmacokinetics, and sampling time. If a large dose is used and the frequency of use is reduced from daily to every other day on those days (e.g., Sunday, Tuesday, and Thursday) preceding the sampling days (rather than randomly assigned), it is possible for the subjects to have positive results all the time. If a homogenous group of heavy daily cocaine users participates in the clinical trial, qualitative urinalysis is less likely to show a statistically significant decrease even though there is a reduction of cocaine use from 7 to 3 times per week (every other day). On the other hand, if the cocaine dose is lower or the cocaine use less frequent, negative results may occur even if there is less than a 60 percent reduction of frequency of cocaine use. In clinical situations, there will be a heterogeneous population and it is likely that statistically significant results can be detected by qualitative analysis if enough subjects are used. Quantitative urinalysis would be more powerful than qualitative urinalysis in clinical trials for detecting reductions in both frequency and in amount.

From the clinical aspect, a period of sustained abstinence, not the reduction of drug amount, might be the most acceptable therapeutic goal. If the efficacy criterion is to demonstrate an increase in the number of days of abstinence, then the only acceptable therapeutic goal is a reduction in frequency, not in daily dose; qualitative urinalysis as the outcome measure would probably be able to meet this goal and quantitative urinalysis would provide only a limited advantage. On the other hand, a reduction in dose only and not frequency would appear to require quantitative analysis.

Currently, the most popular sampling schemes for urine collection are either three times per week (Monday, Wednesday, and Friday) or once a week. This simulation indicates that a three times per week schedule is more powerful than a one time per week schedule in detecting a treatment effect using quantitative urinalysis data. This indication is in agreement with the report by Cone and Dickerson (1992) that the most efficient testing schedule for judging the outcome for a cocaine medication trial would be three times per week.

For qualitative urinalysis, a one time per week sampling schedule could underestimate or overestimate the positive samples compared with the actual data for the three times per week schedule. Because a conservative approach is generally taken for the assessment of clinical efficacy, a three times per week schedule would seem preferable, even though the majority rule approach always provides an artificially higher estimate of percentage positive samples. The use of actual data, which is not commonly practiced in clinical trials, appears to be advantageous and its utility in clinical trials should be considered.

## CONCLUSION

A simple simulation model was used to study the advantages and the limitations of quantitative versus qualitative urinalysis for daily cocaine abusers with an assumed reduction of cocaine use up to 60 percent. In addition, one time per week versus three times per week urine sampling schedules for the assessment of treatment outcomes were compared. The following general conclusions can be made based on this simplified model of simulation:

- Qualitative urinalysis using a cutoff concentration of 300 ng/mL is capable of statistically detecting a reduction in frequency of daily cocaine use, although it is less powerful than that from the quantitative analysis. Qualitative analysis cannot detect significant differences in reduction in the daily amount of use.

- Quantitative urinalysis is capable of detecting reductions both in frequency and amount of cocaine use. Quantitative urinalysis is more sensitive in detecting a reduction in the daily amount than a reduction in the frequency when the reduction is greater than 30 percent.

For quantitative urinalysis, a three times per week urine collection schedule provides more statistical power than does a one time per week collection.

For qualitative urinalysis, the majority rule analysis for a three times per week schedule provides a higher estimate of percentage positive samples than is actually the case. The one time per week schedule could give either higher or lower estimated percentage positive samples. Sampling and analysis of three times per week sampling would seem to be the preferable approach.

Finally, it is abundantly clear from this exercise that an increasing database of actual quantitative clinical urine values will greatly enhance the potential for developing more realistic simulations, which in turn will enhance the design and analysis of outcome data in future clinical trials.

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## APPENDIX

The cumulative amount (M) of benzoylecgonine (BE) excreted in the urine until time *t* is described by the equation (1.48) of Gibaldi and Perrier (1982). The following for M is obtained by rearranging the equation.

$$M = \frac{(k*f*dose)*(km*(1-e^{-k*t})-k*(1-e^{-km*t}))}{k*(km-k)} \qquad (1)$$

Assuming the urine is collected during $t_1$ and $t_2$, t is defined as the midtime between $t_1$ and $t_2$. In this simulation, 9 a.m. is assumed to be the midtime ($t$) and the collection period is assumed to be 2 hours.

$$t_2 - t_1 = 2 \qquad (2)$$
$$t_2 = t + 1 \qquad (3)$$
$$t_1 = t - 1 \qquad (4)$$

The cumulative amount of BE excreted in the two consecutive sampling times, $t_1$ and $t_2$, is given by:

$$M(t_2) = \frac{(k*f*dose)*(km*(1-e^{-k*(t+1)})-k*(1-e^{-km*(t+1)}))}{k*(km-k)} \qquad (5)$$

and

$$M(t_i) = \frac{(k*f*dose)*(km*(1-e^{-k*(t-1)}-k*(1-e^{-km*(t-1)}))}{k*(km-k)} \qquad (6)$$

Amount of BE excreted for the mid-time $t$, $\Delta$ M, is the amount collected during $t_2$ and $t_1$. $\Delta$ M equals to M ($t_2$) - M ($t_1$) and is given by subtracting equation 6 from equation 5.

$$\Delta M = \frac{(k*f*dose)*(km*e^{-(k*t)}*(e^{k}-e^{(-k)})-k*e^{-(km*t)}*(e^{km}-e^{(-km)})}{k*(km-k)} \tag{7}$$

Urinary flow rate is assumed to be 1 mL/min or 0.06 L/hr. The urine volume for the 2-hour interval is (0.06*2). The BE concentration at time $t$ obtained by dividing equation 7 by the urine volume (0.06*2) yields

$$(BE)t = \frac{(k*f*dose)*(km*e^{-(k*t)}*(e^{k}-e^{(-k)})-k*e^{-(km*t)}*(e^{km}-e^{(-km)})}{k*(km-k)*(0.06*2)} \tag{8}$$

# Comparison of Immunoassays for Semiquantitative Measurement of Benzoylecgonine in Urine

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## INTRODUCTION

One way of monitoring the effectiveness of a treatment for cocaine addiction is to analyze a patient's urine at regular intervals for benzoylecgonine (BE), the major metabolite of cocaine. Total absence of BE from the urine indicates that the patient has stopped using cocaine, while a significant reduction in the urinary concentration of BE indicates that the patient is using less cocaine, and therefore is receiving some benefit from the treatment. To determine if there has been a reduction in the amount of cocaine used, it is necessary to employ a quantitative, or at least semiquantitative, method of analysis. However, because many factors can affect the concentration of a drug or any of its metabolites in urine, determination of urine concentrations can only provide an approximate indication of the amount of drug recently introduced into the body.

Analysis of urine for drugs of abuse most often involves an initial screening by an immunoassay to determine the presence or absence of the drug or its metabolites. If the drug is shown to be present by the immunoassay, a quantitative assay is often performed by gas chromatography/mass spectrometry (GC/MS). However, the cost of the GC/MS confirmation assay is high relative to the cost of an immunoassay screening test, and may be prohibitive where multiple specimens from each patient are to be analyzed.

The purpose of this study was to determine the feasibility of using a relatively inexpensive immunoassay to quantitatively determine the concentration of BE in urine from patients undergoing treatment for cocaine addiction.

Three different types of immunoassays were evaluated: (1) an enzyme immunoassay (EIA), (2) a fluorescence polarization immunoassay

(FPIA), and (3) a kinetic interaction of microparticles in solution immunoassay (KIMS). The antibodies used for each of the immunoassays were raised against BE, the major metabolite of cocaine. However, the study included determination of the cross-reactivity of each of the immunoassays to cocaine, ecgonine methyl ester, and ecgonine; each of these compounds can be present in the urine of a cocaine user in significant concentrations, a fact substantiated by quantitative GC/MS measurement of cocaine, norcocaine, BE, ecgonine methyl ester, and ecgonine in 39 urine samples previously shown to be positive for cocaine metabolites.

It was also important to determine the range of BE concentrations that could be measured by each of the immunoassays without performing a dilution, to indicate the number of dilutions that would be required to cover the range of BE concentrations anticipated in the urine from cocaine users.

Finally, the BE concentrations determined by GC/MS in urine samples from cocaine users were compared to the BE concentrations determined by each of the three immunoassays.

## EXPERIMENTAL SECTION

### Immunoassays

The EIA and KIMS analyses were performed at Northwest Toxicology, Inc., on a Hitachi 717 autoanalyzer. The EIA employed the Syva EMIT II cocaine reagents, while the KIMS used the Roche Diagnostics ONLINE cocaine reagents. Both immunoassays were performed according to manufacturers' recommended procedures except that 6-point calibration curves were used (0, 150, 300, 600, 1,000, and 2,000 ng/mL of BE). The FPIA analyses were performed at the Center for Human Toxicology, University of Utah, on an Abbott TDx analyzer using the Abbott TDx cocaine reagents and recommended procedure. For the immunoassay linearity study and the comparison of BE concentrations as determined by each of the immunoassays, samples were analyzed undiluted, after either 1:7 or 1:10 dilutions, and after 1:100 dilutions.

## Gas Chromatography/Mass Spectrometry (GC/MS)

Urine concentrations of cocaine, norcocaine, BE, ecgonine methyl ester, and ecgonine were determined by GC/MS analysis performed at Northwest Toxicology using an extraction procedure similar to that reported in two recent publications (Okeke et al. 1994; Peterson et al. 1995). Deuterium-labeled isotopomers for each of the analytes were added to the urine samples as internal standards. The concentrations of the deuterated internal standards were: BE-$^2H_3$ and cocaine-$^2H_3$, each 100 ng/mL; norcocaine-$^2H_3$, ecgonine methyl ester-$^2H_3$, and ecgonine-$^2H_3$, each 50 ng/mL. The pH of the urine was made acidic by addition of 0.1 M acetate buffer (pH 4.0) and the cocaine and metabolites were extracted on Bond Elute LRC-SCX cation exchange solid-phase columns. The extraction columns were conditioned by washing with 2 mL of methanol followed by 2 mL of 0.1 M acetate buffer. After 1 mL of urine sample was added to each column, the columns were washed with 2 mL of 0.1 M HCl and 4 mL of methanol. The cocaine and metabolites were then eluted with 3 mL of methanol:ammonium hydroxide (98:2) freshly prepared just before using. The metabolites in each extract were derivatized by heating at 70 °C with 100$\mu$L of hexafluoroisopropyl alcohol and 100$\mu$L of pentafluoropropionic anhydride for 30 minutes. The derivatized extracts were then analyzed by GC/MS using a 5 percent phenyl methylsilicone fused silica capillary column (J&W Scientific, DB5MS, 12.5m x 0.2mm ID with a 0.33 µm film thickness) temperature programmed from 135 to 250 °C at 15 °C/min. The analytes were detected by electron ionization with selected ion monitoring performed on a Finnigan SSQ7000 GC/MS system. The ions monitored for each analyte and internal standard and the retention-time windows during which each set of ions was monitored are listed in table 1.

The concentrations of the analytes were determined from the ratio of the peak area of each analyte to the peak area of its corresponding deuterated internal standard; these ratios were compared with 6-point calibration curves that were generated from the analysis of urine fortified with known concentrations of the analytes and the internal standards.

The lower limit of quantitation for each analyte was 5 ng/mL.

**TABLE 1.** *GC/MS data for cocaine, derivatized metabolites, and their internal standards.*

| Analytes and Internal Standards | Retention Time Windows | M/Z of Ions Monitored |
|---|---|---|
| Derivatized ecgonine | 1.0 - 2.15 min. | 318 |
| Derivatized ecgonine-$^2H_3$ | 1.0 - 2.15 min. | 321 |
| Derivatized EME | 2.15 - 3.2 min. | 345 |
| Derivatized EME-$^2H_3$ | 2.15 - 3.2 min. | 348 |
| Derivatized BE | 5.7 - 6.9 min. | 439 |
| Derivatized BE-$^2H_3$ | 5.7 - 6.9 min. | 442 |
| Derivatized norcocaine | 6.9 - 9.0 min. | 105 |
| Derivatized norcocaine-$^2H_5$ | 6.9 - 9.0 min. | 110 |
| Cocaine | 6.9 - 9.0 min. | 303 |
| Cocaine-$^2H_3$ | 6.9 - 9.0 min. | 306 |

## RESULTS AND DISCUSSION

### Benzoylecgonine Concentrations Quantifiable by the Immunoassays

Each of the immunoassays in this study is intended to be used to determine the presence of BE above or below a “cutoff” concentration of 300 ng/mL. To determine the range of linearity of each of the immunoassays, drug-free urine was fortified with known concentrations of BE ranging from 100 ng/mL to 200,000 ng/mL. Each fortified urine sample was analyzed in triplicate by each of the immunoassays using a 5-point calibration curve. Aliquots of each urine sample were also analyzed in triplicate by the EIA and KIMS immunoassays after either 1:10 or 1:100 dilution with drug-free urine. Only undiluted urine aliquots were analyzed by the FPIA. Table 2 compares the BE concentrations determined by each of the immunoassays with the concentrations determined by GC/MS and with the target (weighed-in) concentrations. The concentrations determined by EIA and KIMS in undiluted aliquots were in reasonable

**TABLE 2.** *GC/MS and immunoassay-determined concentrations (ng/mL) in negative urine fortified with benzoylecgonine (BE).*

| BE Target Conc. | GC/MS | EIA | | | KIMS | | | FPIA |
|---|---|---|---|---|---|---|---|---|
| | | Undil. | 1:10 dil. | 1:100 dil. | Undil. | 1:10 dil. | 1:100 dil. | Undil. |
| 100 | 116 | 131 | | | 137 | | | 110 |
| 200 | 235 | 282 | | | 230 | | | 220 |
| 500 | 519 | 620 | | | 531 | | | 550 |
| 1,000 | 1,075 | 1,143 | 1,117 | | 1,038 | 1,047 | | 1,100 |
| 2,000 | 2,147 | | 2,363 | | | 1,893 | | 2,090 |
| 5,000 | 5,175 | | 6,113 | 5,700 | | 4,693 | | |
| 10,000 | 10,096 | | 10,927 | 12,400 | | 8,767 | 10,067 | |
| 20,000 | 20,419 | | | 30,433 | | | 21,067 | |
| 50,000 | 50,454 | | | 71,867 | | | 50,667 | |
| 100,000 | 107,870 | | | 125,000 | | | 97,033 | |
| 200,000 | 266,885 | | | 277,400 | | | 152,100 | |

agreement with the GC/MS-determined concentrations from 100 to 1,000 ng/mL, while the acceptable concentrations determined by FPIA for undiluted aliquots extended to 2,000 ng/mL. By appropriate dilution, the range of acceptable agreement between GC/MS-determined concentrations and the EIA- and KIMS-determined concentrations extend to 100,000 ng/mL. It is reasonable to assume that analysis of diluted aliquots by FPIA would give comparable results.

## Cross-Reactivities of the Immunoassays

To determine the cross-reactivities of each of the immunoassays, drug-free urine was fortified with either cocaine, ecgonine methyl ester, or ecgonine at concentrations ranging from 100 ng/mL to 1 mg/mL. Each fortified urine sample was analyzed in triplicate by each of the immunoassays. Immunoassay responses equivalent to less than 50 ng/mL were considered below the limit of quantitation of the immunoassay and were reported as not detected (ND). The average percent cross-reactivities, calculated by dividing the indicated BE-equivalent concentration by the actual concentration of cocaine or the cocaine metabolite, are listed in table 3.

The percent cross-reactivities for the three immunoassays are similar and are all quite low, particularly at the higher analyte concentrations. Therefore, the measurement of BE in urine should not be significantly affected by cross-reactivity to the concentrations of cocaine, ecgonine methyl ester, and ecgonine, which are likely to be present in urine from cocaine users. The cross-reactivities of the immunoassays to norcocaine were not determined because the concentrations of this metabolite in urine are negligible.

## Concentrations of Cocaine and Its Metabolites in Urine From Cocaine Users

The metabolism of cocaine in man has been extensively studied (Ambre et al. 1988; Jatlow 1988; Jindal and Lutz 1986; Jones 1984; Zhang and Foltz 1990). Ambre reported that after intravenous infusion of cocaine to five subjects, an average of 16 percent of the dose was excreted in the urine as BE, 15 percent as ecgonine methyl ester, and 2 percent as unchanged cocaine. In that study, as in most published investigations of the metabolism of cocaine, ecgonine concentrations were not determined due to analytical difficulties in measuring this very hydrophilic metabolite. In order to gain further insight into the relative concentrations of cocaine

**TABLE 3.** *Cross-reactivities of immunoassays.*

| Spiked Conc. (ng/mL) | Percent Cross-Reactivities | | |
|---|---|---|---|
| | Cocaine | Ecgonine | EME |
| KIMS BE Assay: | | | |
| 100 | ND | ND | ND |
| 200 | ND | ND | ND |
| 500 | ND | ND | ND |
| 1,000 | ND | 5.7% | ND |
| 2,000 | 3.1% | 4.4% | |
| 5,000 | 2.1% | 2.7% | ND |
| 10,000 | 1.8% | 1.8% | ND |
| 20,000 | 1.5% | 1.4% | ND |
| 50,000 | 1.1% | 1.0% | 0.2% |
| 100,000 | 1.0% | 0.9% | 0.1% |
| 200,000 | 1.0% | 1.3% | 0.1% |
| 500,000 | 1.1% | | 0.0% |
| 1,000,000 | | | 0.0% |
| Ave. % Cross-Reactivity = | 1.6% | 2.4% | 0.1% |
| EIA BE Assay: | | | |
| 100 | ND | ND | ND |
| 200 | ND | ND | ND |
| 500 | ND | ND | ND |
| 1,000 | ND | ND | ND |
| 2,000 | ND | ND | ND |
| 5,000 | 1.3% | ND | ND |
| 10,000 | 1.6% | 0.6% | ND |
| 20,000 | 1.7% | 0.7% | ND |
| 50,000 | 1.3% | 0.9% | ND |
| 100,000 | 1.4% | 0.7% | ND |
| 200,000 | 1.2% | 0.9% | ND |
| 500,000 | 1.5% | 0.8% | ND |
| 1,000,000 | 1.4% | 0.7% | 0.0% |
| Ave. % Cross-Reactivity = | 1.4% | 0.8% | 0.0% |

**TABLE 3.** *Cross-reactivities of immunoassays (continued).*

| Spiked Conc. (ng/mL) | Percent Cross-Reactivities | | |
|---|---|---|---|
| | Cocaine | Ecgonine | EME |
| FPIA BE Assay: | | | |
| 100 | ND | ND | ND |
| 200 | ND | ND | ND |
| 500 | ND | ND | ND |
| 1,000 | ND | ND | ND |
| 2,000 | ND | ND | ND |
| 5,000 | ND | ND | ND |
| 10,000 | ND | ND | ND |
| 20,000 | ND | ND | ND |
| 50,000 | 1.6% | 1.5% | ND |
| 100,000 | 1.6% | 1.5% | ND |
| 200,000 | 1.6% | 1.5% | ND |
| 500,000 | | | ND |
| 1,000,000 | | | ND |
| Ave. % Cross-Reactivity = | 1.6% | 1.5% | 0.0% |

and its metabolites in urine from cocaine users, a newly developed GC/MS assay for cocaine, norcocaine, BE, ecgonine methyl ester, and ecgonine was used to analyze urine samples that had been previously found to be positive for cocaine metabolites. Table 4 lists the measured concentrations of cocaine and three of its metabolites in 39 urine samples. Norcocaine was also measured, but its concentrations are not listed in the table because most of them were below the limit of quantitation. The average concentrations of each compound expressed as a percent of the concentration of BE were: cocaine, 3.0 percent; norcocaine, 0.2 percent; ecgonine methyl ester, 19.1 percent; and ecgonine, 46.8 percent. However, the concentrations relative to the concentration of BE varied widely (cocaine, 0 to 16 percent; norcocaine, 0 to 2 percent; ecgonine methyl ester, 0 to 83 percent; and ecgonine, 0 to 215 percent).

## Comparison of Benzoylecgonine Concentrations in Donor Samples Determined by GC/MS and Each of the Immunoassays

Table 5 compares the concentrations of BE in the 39 donor urine samples as determined by GC/MS and by each of the immunoassays.

**TABLE 4.** *GC/MS measured concentrations of BE, cocaine, ecgonine methyl ester, and ecgonine in urine from cocaine users.*

| BE | Cocaine | | EME | | Ecgonine | |
|---|---|---|---|---|---|---|
| (µg/mL) | (µg/mL) | % of BE | (µg/mL) | % of BE | (µg/mL) | % of BE |
| 0.27 | 0.05 | 16.9% | 0.17 | 60.7% | 0.13 | 48.9% |
| 0.29 | 0.04 | 12.1% | 0.24 | 82.7% | 0.20 | 70.2% |
| 0.30 | 0.02 | 6.7% | 0.21 | 69.3% | 0.26 | 85.3% |
| 0.32 | 0.02 | 5.7% | 0.09 | 27.3% | 0.17 | 52.7% |
| 0.34 | <LOQ | 0.0% | <LOQ | 0.0% | <LOQ | 0.0% |
| 0.36 | <LOQ | 0.0% | 0.06 | 17.8% | 0.77 | 215.0% |
| 0.36 | <LOQ | 0.0% | <LOQ | 0.0% | <LOQ | 0.0% |
| 0.38 | <LOQ | 0.0% | <LOQ | 0.0% | 0.01 | 2.9% |
| 0.41 | 0.01 | 3.2% | <LOQ | 0.0% | 0.01 | 2.5% |
| 0.41 | <LOQ | 0.0% | 0.01 | 2.9% | 0.34 | 84.0% |
| 0.45 | 0.01 | 2.4% | 0.07 | 16.1% | 0.30 | 66.7% |
| 0.46 | <LOQ | 0.0% | <LOQ | 0.0% | <LOQ | 0.0% |
| 0.55 | <LOQ | 0.0% | 0.11 | 19.0% | 0.29 | 52.9% |
| 0.69 | 0.01 | 2.0% | 0.09 | 12.9% | 0.35 | 50.5% |
| 0.77 | <LOQ | 0.0% | 0.05 | 7.0% | 0.13 | 16.9% |
| 0.78 | 0.07 | 8.7% | 0.36 | 46.0% | 0.95 | 121.8% |
| 1.02 | 0.10 | 9.8% | 0.20 | 19.6% | 1.44 | 141.2% |
| 1.12 | 0.02 | 1.8% | 0.12 | 10.7% | 1.05 | 93.8% |
| 1.14 | 0.02 | 1.8% | 0.35 | 30.7% | 0.20 | 17.5% |
| 1.22 | 0.02 | 1.9% | <LOQ | 0.0% | 0.04 | 3.0% |
| 1.28 | 0.02 | 1.5% | 0.15 | 12.0% | 0.28 | 21.5% |
| 1.47 | 0.04 | 2.7% | 0.03 | 2.0% | 0.74 | 50.3% |
| 1.54 | 0.03 | 2.1% | 0.12 | 7.6% | 1.07 | 69.5% |
| 1.54 | 0.04 | 2.6% | 0.34 | 22.1% | 0.55 | 35.7% |
| 2.55 | 0.12 | 4.7% | 1.09 | 42.7% | 0.98 | 38.4% |
| 2.73 | 0.24 | 8.8% | 0.23 | 8.4% | 1.32 | 48.4% |
| 2.73 | 0.03 | 1.1% | 0.14 | 5.1% | 0.96 | 35.2% |
| 4.09 | ND | 0.0% | 1.10 | 26.9% | 0.52 | 12.7% |
| 4.95 | ND | 0.0% | 0.20 | 4.0% | 1.02 | 20.6% |
| 5.29 | 0.10 | 1.9% | 0.26 | 4.9% | 2.58 | 48.8% |
| 6.40 | ND | 0.0% | 0.05 | 0.8% | 2.39 | 37.3% |
| 6.60 | 0.16 | 2.4% | 0.98 | 14.8% | 3.15 | 47.7% |

**TABLE 4.** *GC/MS measured concentrations of BE, cocaine, ecgonine methyl ester, and ecgonine in urine from cocaine users (continued).*

| BE | Cocaine | | EME | | Ecgonine | |
|---|---|---|---|---|---|---|
| (µg/mL) | (µg/mL) | % of BE | (µg/mL) | % of BE | (µg/mL) | % of BE |
| 8.44 | 0.09 | 1.1% | 1.77 | 21.0% | 5.23 | 62.0% |
| 9.19 | 0.09 | 1.0% | 0.89 | 9.7% | 2.03 | 22.1% |
| 10.13 | 0.10 | 1.0% | 1.08 | 10.7% | 3.11 | 30.7% |
| 11.74 | 0.09 | 0.8% | 1.97 | 16.8% | 3.17 | 27.0% |
| 14.37 | 0.11 | 0.8% | 2.83 | 19.7% | 2.61 | 18.2% |
| 22.01 | 0.04 | 0.2% | 3.12 | 14.2% | 3.49 | 15.9% |
| 93.81 | 9.67 | 10.3% | 72.55 | 77.3% | 55.09 | 58.7% |
| | | | | | | |
| Average % of BE = | | 3.0% | | 19.1% | | 46.8% |
| Range of % of BE = | | 0 to 16% | | 0 to 83% | | 0 to 215% |

The concentrations shown for the immunoassay determinations are the values obtained from analysis of an undiluted aliquot, or a 1:10 or 1:100 diluted aliquot. The immunoassay-determined concentrations from undiluted urine aliquots were used for samples found by GC/MS analysis to have BE concentrations between 0.1 and 1.0 µg/mL. For samples found by GC/MS to have BE concentrations from 1.0 to 10.0 µg/mL, the immunoassay-determined concentrations from 1:10 diluted aliquots were used, and for samples found by GC/MS to have BE concentrations from 10.0 to 100.0 µg/mL, the immunoassay-determined concentrations from 1:100 diluted aliquots were used. No donor samples were available having BE concentrations above 100 µg/mL. The percent differences between the concentrations determined by GC/MS and each immunoassay are also listed in table 5. The average of the percent differences for each immunoassay and the GC/MS measured concentration was FPIA, -13 percent; EIA, 27 percent; and KIMS, 12 percent. The concentrations of BE determined by GC/MS were plotted against the concentrations determined by the KIMS assay in figure 1. The slope of the linear regression line is 1.003 and the $r^2$ is 0.979. The corresponding plot for EIA versus GC/MS is shown in figure 2; the slope is 1.414 and the $r^2$ is 0.978, and the plot for FPIA versus GC/MS (figure 3) gives a slope of 0.749 and an $r^2$ of 0.907. The data for the sample containing 93.8 ng/mL

**TABLE 5.** *Measured concentrations (µg/mL) of BE in donor samples.*

| BE Conc. | FPIA | | EIA | | KIMS | |
|---|---|---|---|---|---|---|
| by GC/MS | Conc. | % Dif. | Conc. | % Dif. | Conc. | % Dif. |
| 0.27 | 0.30 | 0.10 | 0.37 | 0.36 | 0.38 | 0.40 |
| 0.29 | 0.27 | -0.07 | 0.38 | 0.31 | 0.40 | 0.38 |
| 0.30 | 0.30 | 0.00 | 0.43 | 0.43 | 0.50 | 0.67 |
| 0.32 | 0.44 | 0.40 | 0.48 | 0.52 | 0.50 | 0.59 |
| 0.34 | 0.41 | 0.21 | 0.42 | 0.24 | 0.41 | 0.21 |
| 0.36 | 0.30 | -0.16 | 0.40 | 0.11 | 0.45 | 0.25 |
| 0.36 | 0.31 | -0.14 | 0.37 | 0.03 | 0.34 | -0.06 |
| 0.38 | 0.11 | -0.71 | 0.33 | -0.13 | 0.31 | -0.18 |
| 0.41 | 0.25 | -0.38 | 0.39 | -0.04 | 0.33 | -0.19 |
| 0.41 | 0.51 | 0.25 | 0.69 | 0.70 | 0.64 | 0.57 |
| 0.45 | 0.66 | 0.45 | 0.60 | 0.32 | 0.65 | 0.43 |
| 0.46 | 0.31 | -0.33 | 0.38 | -0.18 | 0.37 | -0.20 |
| 0.55 | 0.65 | 0.17 | 0.92 | 0.66 | 0.81 | 0.46 |
| 0.69 | 0.50 | -0.27 | 0.75 | 0.09 | 0.74 | 0.07 |
| 0.77 | 0.22 | -0.71 | 0.82 | 0.07 | 0.57 | -0.26 |
| 0.78 | 0.77 | -0.01 | 0.80 | 0.03 | 0.85 | 0.09 |
| 1.02 | 0.90 | -0.12 | 0.96 | -0.06 | 1.15 | 0.13 |
| 1.12 | 1.00 | -0.11 | 1.65 | 0.47 | 1.44 | 0.29 |
| 1.14 | 1.80 | 0.58 | 1.79 | 0.57 | 2.09 | 0.83 |
| 1.22 | 0.60 | -0.51 | 1.01 | -0.17 | 1.07 | -0.12 |
| 1.28 | 0.30 | -0.77 | 0.70 | -0.45 | 0.58 | -0.55 |
| 1.47 | 0.70 | -0.52 | 1.91 | 0.30 | 1.94 | 0.32 |
| 1.54 | 0.50 | -0.67 | 1.61 | 0.05 | 1.51 | -0.02 |
| 1.54 | 1.40 | -0.09 | 2.40 | 0.56 | 2.04 | 0.32 |
| 2.55 | 2.50 | -0.02 | 2.85 | 0.12 | 2.32 | -0.09 |
| 2.73 | 2.00 | -0.27 | 3.36 | 0.23 | 2.55 | -0.07 |
| 2.73 | 3.00 | 0.10 | 3.60 | 0.32 | 2.38 | -0.13 |
| 4.09 | 2.20 | -0.46 | 5.45 | 0.33 | 4.50 | 0.10 |
| 4.95 | 5.00 | 0.01 | 7.55 | 0.53 | 6.19 | 0.25 |
| 5.29 | 3.50 | -0.34 | 6.30 | 0.19 | 5.90 | 0.12 |
| 6.40 | 4.50 | -0.30 | 8.11 | 0.27 | 5.31 | -0.17 |
| 6.60 | 5.30 | -0.20 | 9.23 | 0.40 | 7.43 | 0.13 |
| 8.44 | 4.80 | -0.43 | 13.23 | 0.57 | 6.30 | -0.25 |

**TABLE 5.** *Measured concentrations (µg/mL) of BE in donor samples (continued).*

| BE Conc. | FPIA | | EIA | | KIMS | |
|---|---|---|---|---|---|---|
| by GC/MS | Conc. | % Dif. | Conc. | % Dif. | Conc. | % Dif. |
| 9.19 | 11.60 | 0.26 | 11.31 | 0.23 | 10.00 | 0.09 |
| 10.13 | 8.00 | -0.21 | 10.10 | 0.00 | 9.00 | -0.11 |
| 11.74 | 8.00 | -0.32 | 18.20 | 0.55 | 13.70 | 0.17 |
| 14.37 | 7.00 | -0.51 | 17.90 | 0.25 | 13.30 | -0.07 |
| 22.01 | 18.00 | -0.18 | 33.20 | 0.51 | 22.80 | 0.04 |
| 93.81 | 195.00 | 1.08 | 210.70 | 1.25 | 134.60 | 0.43 |
| Average % Difference with | | | | | | |
| GC/MS determined conc. -13% | | | | 27% | | 12% |

of BE (table 5) are not included in the linear regression plots because they strongly biased the correlation determination.

## Limitations to the Interpretation of the Urine Drug and Metabolite Concentrations

In addition to the size of dose and the elapsed time between use of cocaine and collection of the urine, many other factors can affect the concentration of cocaine and its metabolites in urine specimens. They include route of administration, intersubject differences in metabolism, volume of fluid intake prior to giving a urine specimen, and chemical hydrolysis occurring in the urine prior to analysis.

The urine samples were received at Northwest Toxicology as part of its workplace drug-testing business. From the time a urine specimen is collected to the time the testing is completed is typically 3 to 4 days. During this time the specimens are not refrigerated. The donor urine specimens used in this study were stored frozen after they were initially found to be positive for cocaine metabolites. After collecting positive samples over a 4-week period, the immunoassays and GC/MS analyses described here were performed over an additional 4-week period, during which the urine samples were stored at normal refrigerator temperatures. The measured concentrations of BE in these samples decreased by an average of only 2 percent and a maximum of 13 percent from the time the initial GC/MS confirmation was performed until the time the GC/MS determination of cocaine and its four metabolites was performed.

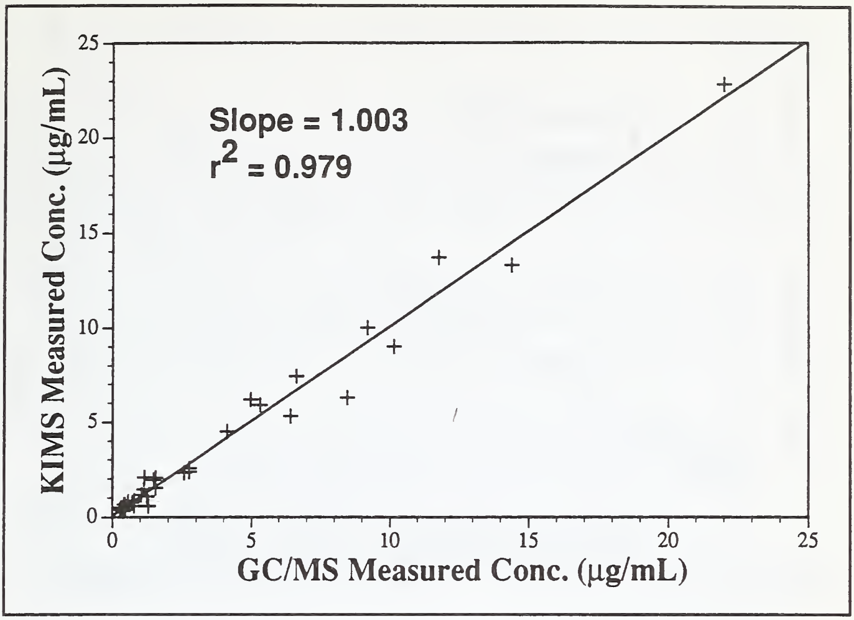

FIGURE 1. *BE concentrations determined by KIMS versus GC/MS.*

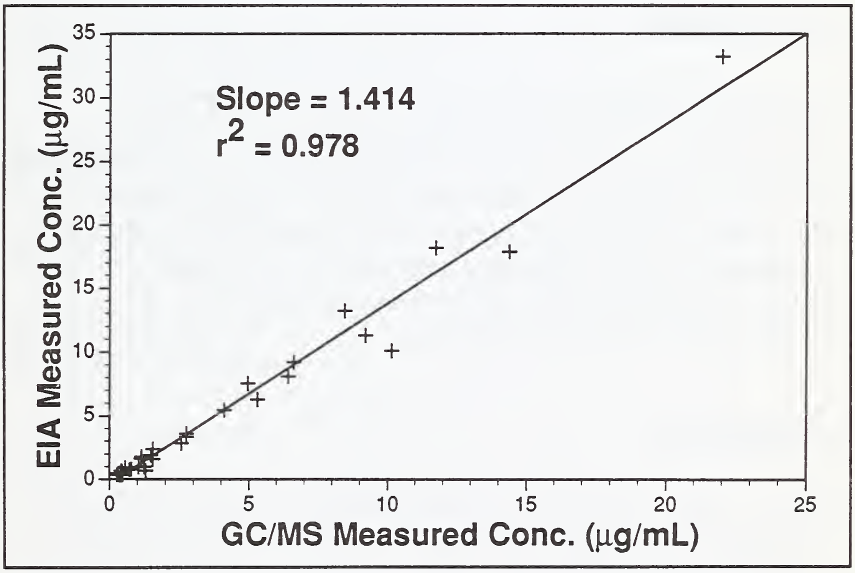

FIGURE 2. *BE concentrations determined by EIA versus GC/MS.*

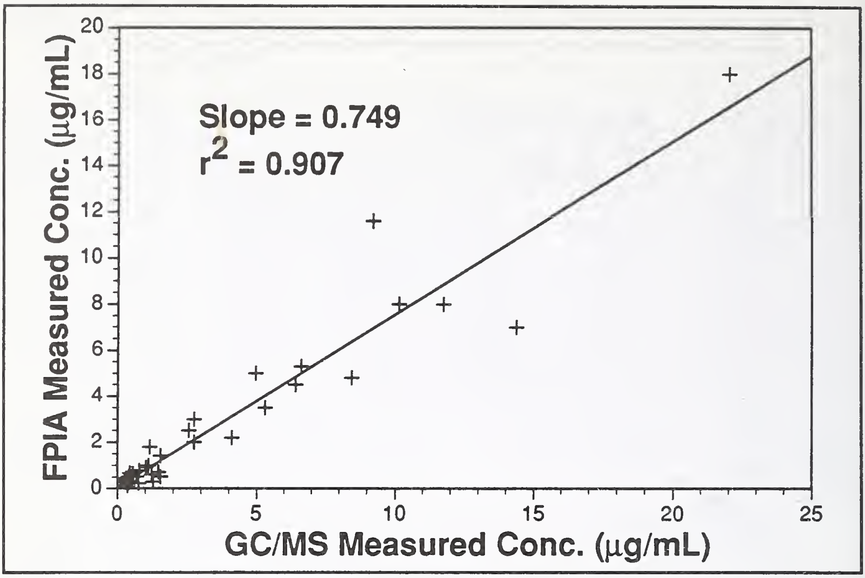

**FIGURE 3.** *BE concentrations determined by FPIA versus GC/MS.*

## CONCLUSIONS

The data presented here show that three commercially available immunoassays can be used with appropriate dilutions to obtain semi-quantitative measurement of BE in urine over a concentration range of at least 0.1 to 1000 µg/mL. Even though cocaine, ecgonine methyl ester, and ecgonine can be present in urine from cocaine users at widely varying concentrations, they have only a minor effect on the immunoassay responses due to their low cross-reactivity to the antibodies used in these immunoassays.

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# Appendix I: Workshop Summary Outcome Measures and Success Criteria

*Betty Tai*

On October 8, 1992, the second Clinical Decision Network workshop sponsored by the Medications Development Division (MDD), National Institute on Drug Abuse (NIDA) was held in Bethesda, Maryland. There were 30 attendees at this workshop (see attachment I). The agenda of this workshop addressed specific issues regarding standardized outcome measures and definitions of success of clinical efficacy trials for cocaine addiction pharmacotherapy. These two issues were identified in an earlier workshop (held April 20-21, 1992) as missing elements in current research and development processes for cocaine addiction pharmacotherapy. The meeting program was divided into two parts. The morning session included brief presentations by invited participants, which provided introduction, overview, background, and objectives of the workshops. Two workshops were conducted during the afternoon session, with participants divided into small groups. Discussions were focused on specific issues regarding using biological markers, e.g., urine, to assess cocaine use (workshop I), and defining abstinence as an outcome measure (workshop II) in conducting clinical efficacy trials.

Workshop I - "Assessment of Drug Use" group 1 was moderated by Richard Hawks and Paul Fudala; group 2 was moderated by Nora Chiang and Reese Jones. Workshop II, "Definition of Abstinence" group 1 was moderated by Peter Bridge and Jeff Wilkins; group 2 was moderated by Frank Vocci and Jim Cornish.

## EFFICACY OUTCOME MEASURES

Participants generally agreed that the outcome measures for assessing the clinical efficacy of cocaine addiction pharmacotherapy should reliably and accurately reflect the benefits of the treatment. A core battery of outcome measures has been proposed by Dr. Charles O'Brien's group. Participants unanimously agreed that urinalysis should be used as an efficacy outcome measure. The advantage of this is obvious, as this is the best of the currently available surrogate markers for monitoring cocaine intake. However, this method has its limitations; therefore, it is important to thoroughly understand the basic pharmacokinetics concepts and analytical methods applied to the urine screening of cocaine exposure to ensure proper experimental design and data analysis. Participants also expressed the desire to have some standardized method of collecting, analyzing, and interpreting urinalysis data so that results may be readily compared across studies.

## USE OF URINE DATA TO ASSESS COCAINE USE BEHAVIOR

Urinalysis of cocaine, benzoylecgonine (BE), or other metabolites is a surrogate measure for cocaine exposure. To use urine data reliably and accurately to estimate actual cocaine use, it is important to fully understand the underlying principles and the current state-of-the-art technology for urinalysis.

### Pertinent Issues

Some of the following issues (the pharmacokinetics of cocaine and the clinical relevance of urinalysis in measuring drug use) were discussed in the workshop, some (the chemical analysis, the sampling scheme of the urine samples, and the trial designs) were not. For the purpose of having a complete record as a general background for later discussion, the author has supplemented some of the information.

*Pharmacokinetics*. Cocaine, whether administered intranasally or intravenously, has a fast onset of action coupled with a speedy rise of plasma cocaine concentration. The bioavailability via the intranasal (IN) route is about 50 to 80 percent and via the smoke route is about 10 to 20 percent. Cocaine has short half-life of about 1.5 hours. BE and ecgonine methyl ester, the major nonactive metabolites of cocaine, have half-lives of 7.5 and 3.5 hours, respectively. Therefore, BE is the most commonly screened target and can be detected in the urine for up to 2 days after the last cocaine use. Depending on the frequency of urine sampling and the pattern of cocaine use (daily use versus binge use), a negative urine sample may not be a clear indication of lack of cocaine use, and a positive urine sample may be due to the carried-over effects of a previous episode 3 to 5 days before sampling.

*Chemistry*. Both immunoassay and chromatography methods have been used to detect urine BE. Immunoassays such as EMIT, RIA, and Abbott

ADX have been popular for qualitative measurements because they are less expensive, have fast turnaround, and are reliable. Generally, 300 ng/mL is set as the cutoff. Results are expressed as positive or negative on the basis of BE concentrations. Recently, some laboratories have been using GC or GC/MS for quantitative assays of BE concentrations in urine. This raises new possibilities for analysis and interpretation of urine data. Extensive discussion on this implication was part of the workshop agenda. Different methods have different sensitivity, specificity, and reproducibility of detection. Therefore, it may be advantageous to have a central laboratory analyze all the samples collected from multisite trials. This becomes critical when considering whether quantitative urine measures would be useful in particular studies.

*Trial Design (Statistics).* Although it was not the focus of discussion at this workshop, design and statistical issues are unavoidable in meaningful discussions about using urinalysis to monitor cocaine intake. Major relevant issues are the design of sampling schemes (random or fixed schedule) used to collect samples, the frequency and timing of sampling, and quantitative versus qualitative analysis of urine data. These issues are critical in designing trials that would minimize the carryover effect and maximize the possibility of detecting cocaine intake. The issue of how to treat missing samples is critical in analyzing urinalysis data. Conservative methods usually count a missing sample as a positive sample. However, justification for such statistical treatment is needed. One strategy is to shorten the trial duration to minimize the missing datapoints.

*Clinical Relevance.* From the above discussions it is clear that there are limitations in using urinalysis data to estimate cocaine use behavior. Generally, urinalysis data are not very sensitive markers because of high variability. It is extremely difficult to use urine data to estimate the frequency and amount of cocaine use. Changes observed in urinalysis data have not been correlated with changes in any other outcome variables such as patients' well-being, employment status, or marital status. Until such correlations are established, the clinical usefulness of urine data is limited to validating reported drug use.

### Urine Data Analysis: Qualitative Versus Quantitative

The current urine analysis methods were developed for detecting illicit drug use in the workplace. For cocaine detection, the urine concentration of BE (a major inactive metabolite with longer half-life) is analyzed by immunoassays. A BE concentration of 300 ng/mL was set as the cutoff point. Any sample with a concentration below 300 ng/mL is a negative sample (a clean urine), any sample with a BE concentration above 300 ng/mL is a positive sample (a dirty urine). This is the qualitative method of cocaine detection, which only provides information on whether a cocaine metabolite is present in the urine sample. Lately, several laboratories have been applying chromatography assays and a fluorescence polarization immunoassay to determine actual urine BE concentrations. Therefore, instead of binary assessments of urine samples as either clean or dirty, it is possibile to evaluate urine data in a continuous, quantitative manner. However, the quantitative urinalysis is more time consuming and costly. The advantages and the limitations of the quantitative urinalysis to project cocaine intake behavior were therefore extensively discussed. There was general consensus that it holds significant promise for use in outcome measures of some trials, but that it may offer limited (or no) advantage in others. Clearly more research is needed to resolve the value of the quantitative approach versus the qualitative approach.

## Urine Data Interpretation

*Reduction in Use.* Traditionally, the treatment goal for addiction disorder is to achieve total abstinence. The idea of accepting reduction in use of abused substance as an interim goal for treatment was new and novel to many workshop participants. However, it was felt that because the outcome for treatment for any group of patients is a continuum, measuring improvement by a reduction in the amount of illicit drug use was not unreasonable. Similar to that for many other incurable diseases, the treatment objective may be to bring symptoms into remission. Fewer episodes of use, or reduction in amount of illicit drug use, certainly is an encouraging sign for treatment success. Treatment success may also be viewed as phases or stages: initially, reduction in use may be the goal; ultimately, reduced use leads to availability for other treatments that leads to abstinence.

Reduction in use means reduced amount or/and frequency of cocaine intake. The latter has a significant implication for intravenous (IV) cocaine users, because this would reduce the risk for HIV exposure and conversion. However, some of the participants pointed out that the validity of the assumption that reduction in cocaine use will lead to abstinence or improved scores on the other Addiction Severity Index (ASI) measures and/or prevent the deterioration due to cocaine addiction has not been established through long-term treatment studies. There was a legitimate difference of opinion as to the prognostic significance of minor reductions in cocaine use, although all participants agreed that major reduction in cocaine use was a good prognostic sign.

With qualitative urinalysis, reduction in use may be expressed collectively in decreased numbers (or percentages) of positive (dirty) samples or increased numbers (or percentages) of negative (clean) samples within a specified study period, and individually as decreased or increased number of days of urine samples being positive or negative. However, in a recent report by Batki and Jones on the effect of fluoxetine on cocaine use, the authors' results showed that with qualitative urinalysis a statistically significant difference was not achieved between the treatment and control, whereas a statistically significant difference was achieved with quantitative urinalysis. This report sparked extensive discussion on how quantitative urinalysis could provide additional information or improve the sensitivity of urine data in assessing cocaine use behavior.

In quantitative urinalysis, if a significant decrease of mean urine BE quantity between the treatment and placebo groups is observed, the following issues need to be addressed: (1) Is the spread (variability) of the data wide or narrow? The data may reflect only a few heavy users who changed their use behavior. (2) Are subjects stratified by their preferred route of cocaine administration? The bioavailability of the smoking route is much lower than those of the IN and IV routes of cocaine administration. (3) Does an X percent decrease in mean urine BE concentration indicate a parallel X percent reduction in the amount of cocaine intake? If not, what is the correlation between the urine data and amount of cocaine use? (4) Should this reduction be interpreted as X percent of the population achieved a certain level reduction of cocaine intake or that everybody in the study reduced the use by X percent? At present, the demonstration of a reduction of mean urine BE quantity is collective information, i.e., it does not reveal the nature of the reduction. Until these issues are addressed, quantitative urinalysis will be more effective in projecting cocaine use only when it is backed up with additional evidence of efficacy.

Participants generally felt that because of the insensitivity of the biological marker as an outcome measure, any statistically significant reduction in the biological marker measure must project a much more pronounced reduction at the behavior level. Participants also suggested that the acceptable reduction criteria must be set at the behavior level rather than at the urine level. In designing the trial, it is important to set a target for reduction, so that the N (number of study subjects) that will give maximal power may be determined.

*Abstinence.* Participants generally agreed on the definition of abstinence as continuously drug-free days; abstinence can be expressed by urinalysis data as continuous clean days. Note that because of intermittent sampling and possible carryover, clean urine days rather than abstinent days are measured. In other words, days of negative urine do not equal days of abstinence. Urinalysis data can only demonstrate clean urine days and cannot tell the difference between a slip and a relapse. A slip is considered a minor instance of use, but a relapse is a return to addiction. As relapse is not defined by the extent of use, but by symptoms of dependence, urinalysis data are therefore not helpful in differentiating the two. No participant was comfortable about judging relapse on the basis of urinalysis data.

Participants agreed that the proper duration for assessing abstinence depends on the addict's cocaine use pattern. For a daily cocaine user, 4 weeks of observation is considered sufficient. However, for a binger, the time for observation needs to be longer. Most participants considered the patient's being able to abstain for 50 percent of the trial duration a significant improvement. An occasional slip is not considered significant.

In summary, abstinence is not a terribly useful concept. The concept of relapse is important but cannot be evaluated with urinalysis data because relapse is defined by the dependence criterion. It is important to establish the baseline use pattern, i.e., daily user versus binge user. Many participants felt that for cocaine abuse, episodes of compulsive use is a more meaningful measure of efficacy than is abstinence.

*Success Criteria.* What kind and magnitude of reduction in use is considered clinically significant? Participants expressed the following opinions:

1. If a 10 percent reduction means everybody in the study reduced cocaine use by 10 percent, it is not significant, but if 1 out of 10 subjects stopped using cocaine, it is significant.

2. A reduction in use from seven to three injections per day is significant because it reduced the risk for HIV transmission.

3. A reduction in use from seven to five injections per day is not impressive, but a reduction from 7 to 5 days per week is impressive.

4. For a daily cocaine user, 1 abstinent day per week is significant. However, for a cocaine binger, days of abstinence do not mean much.

5. The timing of the reduction in use is also important in determining the significance; if the reduction in use occurred at the beginning of the trial and toward the end of the trial, the use pattern returned and the reduction cannot be viewed as effective.

## CONCLUSION

While clear consensus on all the discussion points was an elusive goal, it was clear that much more thought is currently being given to more innovative ways to use urine data for outcome measures in clinical efficacy trials. Researchers are at the stage where new technology allows the generation of relatively quantitative results on urine samples, and such data hold interesting promise for identifying trends in drug efficacy. The many technical, clinical, and statistical issues raised in these discussions has laid critical groundwork for developing standardized approaches to the application of urinalysis for drug abuse pharmacotherapeutics development. Having a marker that could accurately and reliably measure the episodes and amount of each cocaine intake would be ideal.

Unfortunately, current available technology and methods of urine screening do not provide such information. For effective use of urinalysis results as a surrogate outcome measure of the effect of pharmacotherapy on cocaine usage, the participants recommended the following:

1. Urinalysis is a useful objective outcome measure to monitor cocaine usage.

2. The sampling frequency should be appropriate to the objectives of the study; for cocaine, more than once weekly is needed.

3. A baseline measure of use pattern should be established with more than one urine sample and for longer than 1 week.

4. Urine data should be collected in a way that allows quantitative and qualitative analysis and is not dependent on a specific collection hypothesis or analytical plan.

5. The urine data should be investigated at specific points as well as over periods to see if there is a trend of reduction. If a trend is noted, what is the timecourse of the reduction? Is the reduction at the beginning or the end of the trial?

6. Self-reports, which provide information of timing, episodes, and amount of use, should be collected along with urine samples.

7. All urine data should be evaluated for the individual as well as the group, because there will be some who stopped use, some who reduced use, some who did not change. For those who have reduced or stopped use, other signs of improvement (employment, marriage, etc.) should be examined to see if there is any correlation.

8. When submitted for Food and Drug Administration (FDA) review (according to Dr. Curtis Wright), the urine data should be collected, analyzed, and summarized in the most straightforward way possible. In some cases it may be advantageous to have the clinician evaluate the urine data while the trial is still blind, integrating the urine toxicology with the clinical reports. In other cases it may be best to keep the urine data confidential during the double-blind period. In either case, rules for collection procedures, attribution of missing samples, handling of dropouts, and the proposed analysis should be specified in advance.

## ATTACHMENT I

### Participant List

The participants of the workshop are listed below. Many of them have read and commented on this summary report. However, the choices of what to incorporate and how to present the materials are those of the author, who, therefore, takes full responsibility for any errors.

Tanya Alim, M.D.
George Bigelow, Ph.D.
Jack Blain, M.D.
Peter Bridge, M.D.
Nora Chiang*, Ph.D.
James Cornish, M.D.
Everett Ellinwood, M.D.
Marian Fischman, Ph.D.
Paul Fudala, Ph.D.
Donald M. Gallant, M.D.
Charles Grudzinskas*, Ph.D.
Sue Herbert, M.A., R.N.
Richard Hawks*, Ph.D.
Reese Jones*, M.D.
Thomas Kosten, M.D.
Frances Levine, M.D.
Walter Ling, M.D.
Juri Mojsiak, D. Pharm.
Jack Mendelson, M.D.
Ann Montgomery, M.S., R.N.
Charles O'Brien, M.D., Ph.D.
Kenzie Preston, Ph.D.
Adel Roman, R.N.
Doralie Segal, M.S.
Charles Schuster, Ph.D.
Betty Tai, Ph.D.
Jeffery Wilkins, M.D.
George Woody, M.D.
Curtis Wright*, M.D., M.P.H.
Frank Vocci*, Ph.D.

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* = Participants who have read and commented on the summary report.

# Appendix II: Workshop Summary Clinical Decision Tree for Cocaine Addiction Pharmacotherapy

*Betty Tai, Charles V. Grudzinskas, Peter Bridge, and Nora Chiang*

A coherent research and development (R&D) plan to effectively and efficiently move compounds into multicenter efficacy trials for cocaine addiction pharmacotherapy does not exist at present. In light of this, in 1992, the Medications Development Division (MDD) of the National Institute on Drug Abuse (NIDA) sponsored three Clinical Decision Network workshops to identify, investigate, and develop actions that would facilitate the development of such a plan. From the first workshop, it was identified that the key missing element is the lack of a clinical decision tree that provided guidance in critical decisionmaking regarding the selection, prioritizing, and discontinuation/ elimination of compounds from the R&D process. In subsequent workshops (held on November 13, 1992) proposals were reviewed to address these issues, and a clinical decision tree (see figure 1) was developed with the following key features: (1) an assumption that the investigational compounds are with or without a strong clinical pharmacology model (table 1); (2) if the compound has a strong clinical pharmacology model, then the development rationale, the initial safety, pharmacokinetics, and interaction with abused substances may be tested in a human laboratory settings (table 2), if not other proper hypothesis-generating trials; and (3) for all compounds, the efficacy confirmation trials may be tested with designs specific to the proposed indication (table 3).

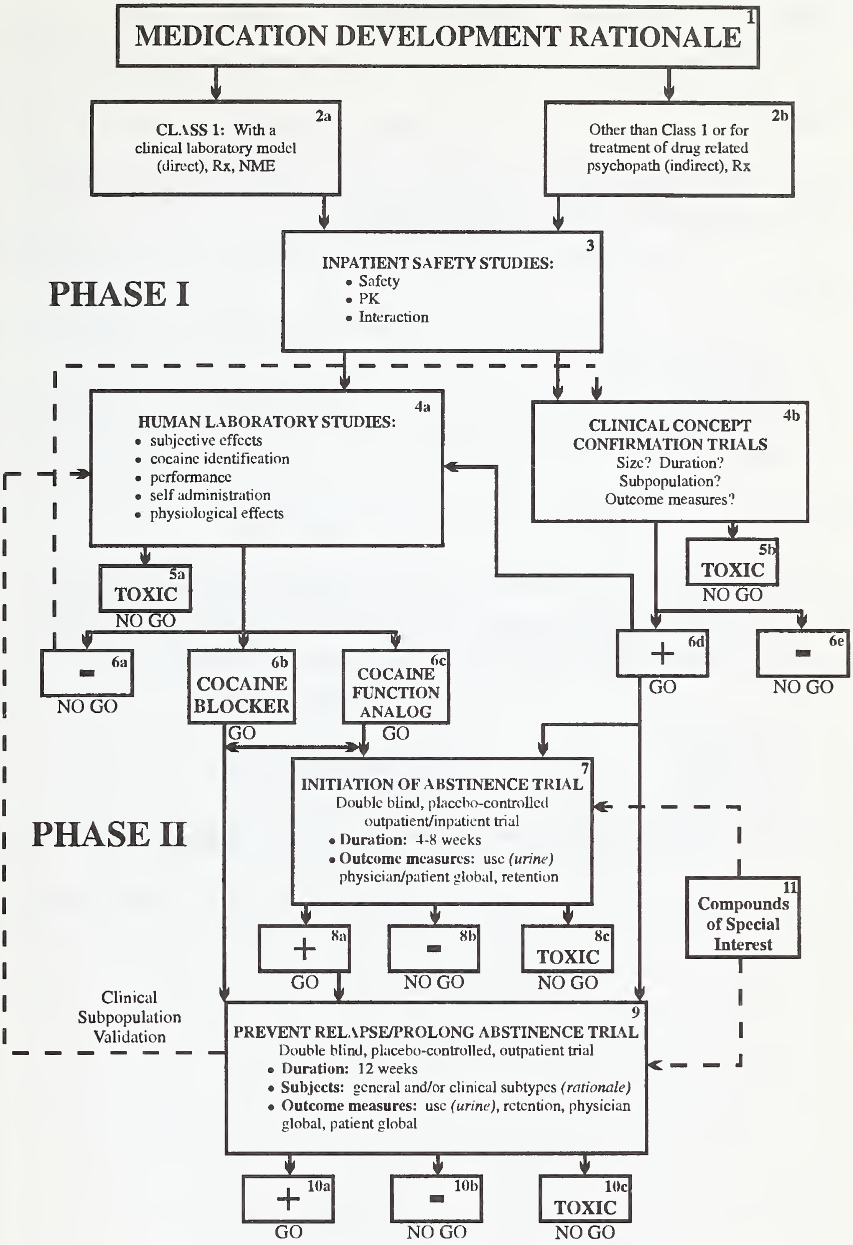
MEDICATION DEVELOPMENT RATIONALE
1
CLASS 1: With a clinical laboratory model (direct), Rx, NME
2a
Other than Class 1 or for treatment of drug related psychopath (indirect), Rx
2b
PHASE I
INPATIENT SAFETY STUDIES:
• Safety
• PK
• Interaction
3
HUMAN LABORATORY STUDIES:
• subjective effects
• cocaine identification
• performance
• self administration
• physiological effects
4a
CLINICAL CONCEPT CONFIRMATION TRIALS
Size? Duration?
Subpopulation?
Outcome measures?
4b
TOXIC
5a
NO GO
TOXIC
5b
NO GO
-
6a
NO GO
COCAINE BLOCKER
6b
GO
COCAINE FUNCTION ANALOG
6c
GO
+
6d
GO
-
6e
NO GO
PHASE II
INITIATION OF ABSTINENCE TRIAL
Double blind, placebo-controlled outpatient/inpatient trial
• Duration: 4-8 weeks
• Outcome measures: use (urine) physician/patient global, retention
7
+
8a
GO
-
8b
NO GO
TOXIC
8c
NO GO
Compounds of Special Interest
11
Clinical Subpopulation Validation
PREVENT RELAPSE/PROLONG ABSTINENCE TRIAL
Double blind, placebo-controlled, outpatient trial
• Duration: 12 weeks
• Subjects: general and/or clinical subtypes (rationale)
• Outcome measures: use (urine), retention, physician global, patient global
9
+
10a
GO
-
10b
NO GO
TOXIC
10c
NO GO

**FIGURE 1.** *Clinical Decision Tree.*

**TABLE 1.** *Characteristics of compounds.*

---

**Class 1**

With a clinical laboratory testing model (e.g., substitute/replace, block cocaine transporter, monoamine receptors, etc.)

Sources

- Drug discovery
- Champion
- Rx experience
- Special class

**Class 2**

Other than Class 1 or for the treatment of underlying psychopathology (e.g., reverse/normalize neuropharmacologic function or treat specific clinical problems associated with cocaine abuse/dependence, etc.)

- Rx experience
- Champion
- Special class

---

**TABLE 2.** *Phase I: Human laboratory studies.*

| | |
|---|---|
| OBJECTIVES | Safety dose range<br>Activity dose response<br>Interaction of cocaine and testing compound |
| SUBJECTS | General cocaine-experienced volunteers |
| DURATION | 1 day to 2 weeks |
| SETTING | Laboratory |
| OUTCOME MEASURES | (Cocaine alone, cocaine + test medication)<br>**Safety:**<br>CV, behavior, mood<br>**Subjective effects:**<br>ARCI, POMS, VASS, liking/craving<br>**Drug stimulus**<br>**Self-administration:**<br>Free access, choice |

Adapted/modified from abuse liability testing.

**TABLE 3.** *Phase II: Clinical efficacy /safety studies.*

| | |
|---|---|
| OBJECTIVES | Indication specific<br>• Efficacy for initiating abstinence<br>• Efficacy for relapse prevention or prolonging abstinence |
| SUBJECTS | Cocaine dependents stratified by:<br>• Severity<br>• Use pattern<br>• Comorbidity |
| DESIGN | Randomized control trial (RCT) |
| DURATION | 1. 4 to 6 weeks<br>2. 8 to 12 weeks |
| SETTINGS | Inpatient or outpatient |
| OUTCOME MEASURES | **Safety:**<br>CV, behavior, physiologic state, serum chemistry, etc.<br>**Efficacy:**<br>Drug use - self-report, biologic markers<br>Retention in treatment<br>Patient self-assessment<br>Physician assessment |

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